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CONTENTS OF PREVIOUS NUMBER

MAY, 1927. NUMBER 5

Weight and Physical Measurements After Thyroidectomy: Rapid Changes in Weight Reflected in Physical Measurements on Adults After Thyroidectomy. W. R. Miles, Ph.D., Stanford University, Calif., and H. F. Root, M.D., Boston.

Antithrombin Test in Typhoid Fever: Improvements in Technic. C. A. Mills, M.D., Peking, China.

Present Status of Curability of Bronchial Asthma, with Replies to a Questionnaire. Morris H. Kahn, M.D., New York.

Etiologic Factors in Diabetes: Paper II. Joseph H. Barach, M.D., Pittsburgh.

Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women: Redeterminations of Color Index, Volume Index and Saturation Index Standards Based on Observations in One Hundred Cases. Edwin E. Osgood, M.D., and Howard D. Haskins, M.D., Portland, Ore.

Metabolic Studies in the Treatment of Polycythemia Vera with Phenylhydrazine. L. D. Huffman, M.D., Rochester, Minn.

Studies in Acromegaly: IV. The Basal Metabolism. Harvey Cushing, M.D., and Leo M. Davidoff, M.D., Boston.

Addison's Disease and Diabetes Mellitus Occurring Simultaneously: Report of a Case. John H. Arnett, M.D., Philadelphia.

Congenital Ventricular Septal Defect in a Man, Aged Seventy-Nine. Edward Weiss, M.D., Philadelphia.

Some Conditions Affecting Subjective and Objective Manifestations of Hunger: Hunger Sensation Giving Rise to a Marked Respiratory Change. Frederick Hoelzel and Nathaniel Kleitman, Chicago.

Severe Chronic Glomerular Nephritis, Without Hypertension, Cardiac Hypertrophy of Retinal Changes: Report of Two Cases. Edwin G. Bannick, M.D., Rochester, Minn.

Book Reviews.

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STUDIES IN ACROMEGALY

VI. THE DISTURBANCES OF CARBOHYDRATE METABOLISM *

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AND

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BOSTON

CONTENTS

Introduction
Incidence
Etiology
A. The neurogenic explanations
B. The endocrine explanation
Thyroid, suprarenals, pancreas and hypophysis
The Relation of the Pancreas to Glycosuria
The Relation of the Hypophysis to Glycosuria
Counteraction of pituitary extracts and insulin
Sugar Tolerance Tests of Acromegalic Patients Without Glycosuria
The Course and Prognosis of Acromegalic Diabetes
The Effect of Operations on Sugar Tolerance in Acromegaly
A. With existent melituria
B. With hyperglycemia in the absence of melituria
Summary and Conclusions

INTRODUCTION

In preceding papers in this series the subject which we here propose to discuss more in detail has already been touched on. It has been stated [1] that in our series of 100 personally observed cases of acromegaly one out of four has shown glycosuria, and approximately one out of eight proved to have clinically outspoken diabetes mellitus. It has also been stated, in a report dealing with the postmortem observations in four of these cases,[2] that one of the patients had apparently recovered from

* From the Surgical Clinic of the Peter Bent Brigham Hospital, Boston.

1. Davidoff, L. M.: Studies in Acromegaly: II. Historical Note, Endocrinology **10**:453, 1926; III. The Anamnesis and Symptomatology in 100 Cases, Endocrinology **10**:461, 1926.

2. Cushing, H., and Davidoff, L. M.: Studies in Acromegaly: V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of their Significance, Monograph 22, Rockefeller Inst. M. Research, 1927.

severe diabetes, whereas another had died in diabetic coma, the pancreatic islets in both of these cases having been regarded as histologically normal.

In another paper [3] we have ventured to discuss the question of the increased basal metabolic rate in acromegaly and have been inclined to interpret it as primarily of hypophysial origin, even though the thyroid may play a secondary rôle. The same or similar questions arise in regard to the diabetes of acromegaly. Is it primarily hypophysial and secondarily pancreatic, or are the two maladies—one hypophysial and the other pancreatic—merely coincidental? In either case, does the diabetes of acromegaly behave and run the same course as does the more common form of diabetes? An effort to answer these questions will be made in the present communication.

Incidence.—The frequency of diabetes mellitus in acromegaly has been variously estimated. Arnold [4] found 9 per cent of diabetic cases in his review of fifty-six cases from the literature; Hansemann [5] found approximately 12 per cent among ninety-seven reported cases; and Hinsdale [6] found 11 per cent in 130 cases. Borchardt,[7] on the other hand, in a tabulation of 176 cases recorded up to 1908, found sixty-three (35.5 per cent) to have frank diabetes and eight more to have alimentary glycosuria showing a lack of carbohydrate metabolism in approximately 40 per cent of all cases.

The variability of these percentages doubtless depends a good deal on what the compiler of the statistics has been willing to accept as "diabetes mellitus." Borchardt was dealing, up to 1898, with practically the same reported cases of acromegaly that were studied by Hinsdale, and it is hardly likely that the incidence of diabetes in the disease had more than trebled between 1898 and 1908. For purposes of emphasis he may have been tempted to include as examples of diabetes some which others might question. In our series of personally observed cases the percentage that showed indubitable diabetes proves to be the same as that reported by Hansemann.

It, however, is undoubtedly true that if our 100 acromegalic patients had been under constant surveillance, melituria would have been observed in more than 25 per cent of them. Indeed, four of the twelve with frank diabetes showed no evidence of the disease during their first hospital sojourn, and only because they happened to be observed again at a later

3. Cushing, H., and Davidoff, L. M.: Studies in Acromegaly: IV. The Basal Metabolism, Arch. Int. Med. **39:** (May) 1927.

4. Arnold, J.: Weitere Beiträge zur Akromegaliefrage, Virchows Arch. f. path. Anat. **135:**1, 1894.

5. Hansemann, D.: Ueber Akromegalie, Berl. klin. Wchnschr. **34:**417, 1897.

6. Hinsdale, G.: Acromegaly (Boylston Prize Essay), Medicine **4:**441, 1898.

7. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66:**332, 1908.

date was this complication disclosed. Furthermore, the fact, to be discussed later, that acromegalic patients, even in the absence of glycosuria, are apt to show a slight hyperglycemia, may indicate a predisposition on the part of most victims of the disease toward the development of diabetes.

Even should we accept the incidence of true diabetes in association with acromegaly as no higher than 12 per cent, the percentage is far greater than with any other known disorder. One naturally looks, therefore, for some single etiologic factor which might account for this peculiar association of two clinically distinctive maladies.

ETIOLOGY

Several hypotheses have been advanced for the glycosuria so often an accompaniment of acromegaly. They may be divided under two headings: (*a*) the neurogenic and (*b*) the endocrine.

A. The Neurogenic Explanations of the Glycosuria.—There are two of them. One ascribes the complication to pressure of the hypophysial tumor against a predicated sugar center in the hypothalamus; the other ascribes it to some autonomic nerve impulses possibly of emotional character. The first view, which was advanced nearly thirty years ago,[8] has gained such general credence in textbooks that Dock even makes the statement:[9] "Diabetes is most marked with the largest [pituitary] tumors." So far as we can see, there is nothing whatever to support this hypothesis.

That there are important centers in the hypothalamic region which have some bearing on the production of the other variety of diabetes, has been conclusively shown by Camus and Roussy,[10] and by Bailey and Bremer[11] from this clinic. But diabetes insipidus and diabetes mellitus are merely symptoms (one tasteless and one sweet, as pointed out by Thomas Willis) of two disorders which have no possible etiologic relationship, and it is unfortunate that they should continue to carry the same family name. It nevertheless is curious that they should come to be discussed together in connection with the disease acromegaly.

Of the two forms of diabetes, diabetes insipidus, though the rarer, is far more entitled to be considered as a hypophysial or parahypophysial symptom than is diabetes mellitus. But when one considers that diabetes insipidus is practically unknown as a complication of

8. Loeb, L.: Beiträge zur Lehre von Diabetes Mellitus, Centralbl. f. innere. Med. **9**:893, 1898.

9. Dock, G.: The Pituitary Body, in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1915, vol. 4, p. 812, Chapter XXI.

10. Camus, J. E., and Roussy, G.: Experimental Researches on the Pituitary Body, Endocrinology **4**:507, 1920.

11. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

pituitary adenomas, whether acromegalic or hypopituitary, no matter how large they grow to be or how much they may chance to deform the infundibulum and third ventricle, we may well pause before ascribing diabetes mellitus to the pressure of a pituitary adenoma against some still more hypothetical nerve center in the neighborhood. And of this we may speak the more emphatically since the far more numerous chromophobe adenomas of comparable size are rarely accompanied by glycosuria.[12]

In short, the size of tumor and the pressure against the brain as a cause of the diabetes can be entirely discounted. The essence of the matter lies in the fact that only one particular variety of adenoma, irrespective of its size, is prone to cause the disturbance of sugar metabolism which may go on to the production of diabetes mellitus. This particular kind of adenoma is that composed of chromophilic cells which accompanies acromegaly.[13]

One, however, cannot dismiss the hypophysial polyurias and, more particularly, the encephalic glycosuria in quite so summary a fashion. It has long been known that a transient glycosuria is a frequent accompaniment of basal fractures of the skull which may possibly be due, as one of us pointed out,[14] to a coincidental contusion of the pituitary body. Some recent studies by Davidson and Allen [15] have shown that even in the absence of glycosuria, determinations of blood sugar on patients after injuries of the head show a temporary relative intolerance for glucose. All those, moreover, who have undertaken to perform experimental hypophysectomies will have observed that certain of the animals show a transient postoperative glycosuria whether or not they subsequently develop the prolonged and excessive polyuria resembling clinical diabetes insipidus. We have learned from the time of Bernard that various piqûres evoke glycosuria, and we also know that emotional

12. Anders and Jameson *(Am. J. M. Sc.* **148**:323, 1914) report several such cases, but most of them showed only a slight transient glycosuria or a terminal one associated with increased intracranial pressure. One case of hypopituitarism with true diabetes was reported by Sainton and Rol *(Rev. neurol.* **25**: 785, 1913), and they quote a similar observation by Debove. Rare case reports of diabetes coincidental with unusual lesions of the hypophysis such as gumma (Cushing, 1912) or tuberculoma (Lucien et Parisot, 1909) are too infrequent and bizarre to be of significance in this discussion. Whereas 25 per cent of the 100 acromegalic patients in the Brigham Hospital series showed or had a history of melituria, only four of 168 patients with hypopituitary symptoms and a surgically verified chromophobe adenoma either showed or gave a history of melituria.

13. Bailey, P., and Davidoff, L. M.: Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly, Am. J. Path. **1**:185, 1925.

14. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, p. 265.

15. Davidson, E. C., and Allen, C. I.: The Blood Glucose Curve in Head Injuries, Bull. Johns Hopkins Hosp. **37**:217, 1925.

impulses may serve to produce a hyperglycemia with the discharge of sugar, but it is hardly to be believed that the diabetes of acromegaly is due to any such cause or causes.

B. The Endocrine Explanation of the Glycosuria.—Under this heading we must consider the thyroid, suprarenals, islets of Langerhans and hypophysis as possible agents which independently of one another, or together, may disturb the carbohydrate metabolism of the body.

The notion that an increased activity of the thyroid is responsible for acromegalic diabetes mellitus was first expressed by Lorand [16]; and, to be sure, not only is an enlarged thyroid common in acromegaly, but the increased metabolism so often seen might be regarded as an additional evidence of hyperthyroidism. But diabetes mellitus is not a common complication of hyperthyroidism even though transient glycosurias and a tendency toward hyperglycemia are frequently observed; nor does the reverse condition, myxedema, experimental or clinical, show an increase of carbohydrate tolerance in any way comparable to the marked increase seen in experimental or clinical hypopituitarism. What is more, the enlarged thyroid in acromegaly is usually of the inactive or colloidal type.

We consequently may disregard the thyroid as a possible primary agency; and no more does the suprarenal deserve serious consideration, for though the suprarenal cortex hypertrophies in acromegaly, it is the product of the medullary substance, epinephrine, which, under the influence of the autonomic nervous system, is capable of mobilizing sugar with the production of a transient glycosuria.

We may therefore confine ourselves to the hypophysial and pancreatic aspects of the subject in an attempt to answer the question propounded in the introductory paragraphs as to whether acromegalic diabetes differs appreciably from the primarily pancreatic form of the malady.

The senior author in collaboration particularly with Goetsch and Jacobson,[17] and Jacobson and Weed,[18] was engaged for several years in the elusive pursuit of the hypophysial glycosuric and nonglycosuric polyurias. These studies were undertaken after it had been observed that a temporary glycosuria was apt to follow a hypophysectomy, and it was at the time [19] anticipated that the animals would continue to show

16. Lorand, A.: Pathogénie du diabète dans l'acromégalie, Compt. rend. Soc. de biol. **56**:554, 1904.

17. Goetsch, E.; Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Bull. Johns Hopkins Hosp. **22**: 165, 1911.

18. Weed, L. H.; Cushing, H., and Jacobson, C.: Further Studies on the Rôle of the Hypophysis in the Metabolism of the Carbohydrates, Bull. Johns Hopkins Hosp. **24**:40, 1913.

19. Cushing, H.: The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism, J. A. M. A. **53**:249 (July 24) 1909.

a lowered assimilation limit for sugars as a consequence of the operation. Much to our surprise, quite the reverse effect was observed, for the hypophysectomized animals gradually acquired a high sugar tolerance and often showed slight hypoglycemia.[20] This, to be sure, is what might have been expected if the experimental states of hypopituitarism are the reverse of acromegaly, in which, as we now know, glycosuria and hyperglycemia are common. But at the time these studies were under way this was not very clear, and the possible mistake was made of ascribing the disturbance of sugar metabolism to a posterior rather than to an anterior lobe effect.

Certain other experiments were undertaken which showed that an experimentally induced hyperglycemia, brought on by removal of a large portion of the pancreas, tended to subside when a partial hypophysectomy was subsequently performed; and, conversely, that when animals had acquired a high sugar tolerance with hypoglycemia after hypophysectomy, they bore the removal of a large portion of the pancreas with less disturbance to their carbohydrate balance than would the normal animals. Since these observations suggested a close interrelation of an opposing sort between the hypophysis and the pancreatic islets, it was stated[17]: "If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the secretion of the hypophysial posterior lobe [sic] greatly enhances their power in this respect." In other words, it was appreciated that extracts of the pancreatic islets and of the hypophysis should theoretically at least counteract each other in their metabolizing effect on the carbohydrates. Let us consider this matter first from the standpoint of the pancreas.

RELATION OF THE PANCREAS TO THE ACROMEGALIC GLYCOSURIAS

Unfortunately, the universally accepted view that the islets of Langerhans are functionally deranged in pancreatic diabetes has not as yet found its anatomic counterpart, or at least one which is wholly satisfactory. Cecil[21] in a study of the pancreas in ninety cases describes the finding of lesions of one sort or another in 88 per cent of them. Fibrosis of varying degrees was present in seventy-six cases, hyaline degeneration in twenty-seven, lymphocytic infiltration in nine, and hypertrophy in thirty-four cases. A recent report of twenty-six personally studied autopsies leads Root and Warren[22] to admit that, "No one distinctive

20. Crowe, S. J.; Cushing, H., and Homans, J.: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp. **21**:127, 1910.

21. Cecil, R. L.: A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, J. Exper. Med. **11**:266, 1909.

22. Root, H. F., and Warren, S.: A Clinical and Pathologic Study of Twenty-Six Cases of Diabetes, Boston M. & S. J. **194**:45, 1926.

lesion of the islands was found." They, however, describe varying degrees of hyalinization in half of the cases, some sclerosis and lymphocytic infiltration in five others, and in three an adenomatous enlargement. Nevertheless, there is no gainsaying that the pancreas must often be thoroughly searched to find these lesions and, even when found, apparently normal islets may exist alongside of those affected.

Even less definite if anything have been the descriptions of the histopathologic lesions of the pancreas in acromegalic diabetes as reported in the literature. Some of the early and much quoted autopsy reports, to be sure, such as those by Hansemann,[23] Dallemagne[24] and Pineles,[25] record pancreatic lesions; but these lesions consisted merely of an increase in the interlobular connective tissue which is not at all incompatible with normally functioning islets. How little bearing these sclerotic changes have on the subject is well illustrated by two of the carefully studied cases reported by Fraenkel, Stadelmann and Benda;[26] one of them showed no clinical diabetes, but at autopsy had a marked interlobular sclerosis of the pancreas; whereas the other had marked clinical diabetes, died in diabetic coma, and a perfectly normal pancreas was found post mortem. Pathologic evidence prior to Opie's discovery in 1901 is, however, at the best of little value.

Specific reference to the condition of the pancreatic islets in the report of cases of acromegaly with diabetes which have come to autopsy has been rare. One of the earliest references to the subject appears to have been made by Norris[27] who described an adenoma-like hypertrophy; and Kraus[28] reported a case of long standing, in which definite sclerosis of the islets was disclosed. In a previous paper in this series,[2] we have described the findings in two of our own cases. One of the patients had apparently recovered from severe diabetes; the other had died in diabetic coma. In both, the islets had been pronounced normal by competent pathologists. A reexamination of the sections at the present time shows that the islets in the recovered cases are perhaps hypertrophic, and in the case of the patient who died in coma one singe islet shows

23. Hansemann, D.: Die Beziehungen des Pankreas zum Diabetes, Ztschr. f. klin. Med. **26**:191, 1894.

24. Dallemagne, M.: Trois cas d'acromégalie avec autopsie, Arch. de méd. expér. et d'anat. path. **7**:589, 1895.

25. Pineles, F.: Die Beziehungen der Akromegalie zum Myxodem und so anderen blutdrüsener Krankungen, Volkmann's Samml., N. F., 1899, no. 242, p. 1421.

26. Fraenkel, A.; Stadelmann, E., and Benda, C.: Klinische und anatomische Beiträge zur Lehre von der Akromegalie, Deutsche med. Wchnschr. **27**:513, 536, 564, 1901.

27. Norris, C.: A Case of Acromegalia, Proc. New York Path. Soc. **7**:19, 1907-1908.

28. Kraus, E. J.: Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zueinander unter normalen Verhältnissen und in Tumoren, Beitr. z. Path. Anat. u. z. allg. Pathol. **58**:159-210, 1914.

what may possibly be a strand of sclerosis—certainly nothing in either case on which a diagnosis of existent or preexistent diabetes could definitely be based. Of course death in diabetic coma by no means signifies that the patient had, at the time, advanced diabetes, and the absence of pathologic changes therefore does not mean much in a single case.

It is conceivable that the oversecretion of the hypophysial substance may indirectly produce glycosuria in one of two ways: (1) by neutralizing the secretion of the islet tissue in circulation, thereby causing compensatory hypertrophy with ultimate exhaustion of the cells of Langerhans leading to the degenerative changes with which we are familiar, or (2) by actually checking the secretory function of the islets which might possibly lead to no histopathologic changes. However this may be, it seems wholly improbable that the diabetes in acromegaly is due to an independent and coincidental lesion, functional or otherwise, of the pancreatic islets.

TABLE 1.—*Blood Sugar*

	Case 1	Case 2	Case 3	Case 4
Fasting	0.38%	0.280%	0.13%	0.15%
	20 units insulin subcutaneously	10 units insulin intravenously*	20 units insulin subcutaneously	20 units insulin subcutaneously
After 2 hours	0.27	0.227	0.10	0.109
After 4 hours	0.25	0.189	0.10	0.093

* This patient had breakfasted after the fasting blood test.

If it is to be assumed, then, that in the state of hyperpituitarism a substance antagonistic to insulin is thrown into the circulation, it must also be assumed that any additional insulin supplied to a patient with acromegalic diabetes will serve to lower the blood sugar just as it would in ordinary diabetes; in other words, it would overcome the action of the excessive pituitary secretion. To test this, observations in four acromegalic patients with diabetes were carried out in the following manner: Fasting blood sugar determinations were made, insulin was injected and the blood sugar quantitated at varying intervals afterward.[29] The results are shown in table 1.

Dr. Fitz has expressed doubt as to whether the fall in the sugar percentage in one or two of these cases has been as significant as he would have expected in ordinary diabetes. Blum and Schwab,[30] on the other hand, made a similar test on two diabetic patients, one with

29. The sugar determinations according to the method of Folin and Wu have been made for us in the laboratory of our colleague, Dr. Reginald Fitz, to whom we wish here to express our great indebtedness not only for this service but also for his continued interest and helpfulness in other matters relating to the problem of these glycosurias.

30. Blum, L., and Schwab, H.: Diabète acromegalique et insuline, Compt. rend. Soc. de biol. **89**:195, 1923.

acromegaly and one without, and found that the sugar content of the blood became reduced just as promptly and effectively in the acromegalic as in the other patient. We may therefore conclude that insulin acts favorably on the hypophysial as well as on the pancreatic form of the disease, but whether the diabetes of acromegaly is as definitely controlled by insulin is questionable. To this we shall return.

Observations on the possible reciprocal action of pancreatic lesions on the hypophysis have been reported by several writers, but the results have been conflicting. Mention has been made of the experiments by Goetsch, Cushing and Jacobson [17] in which histologic changes, particularly shown by an increased cellularity of the posterior lobe, were described as a consequence of subtotal pancreatectomies. The observations were thought to indicate a hypertrophic reaction.

The same authors, as previously stated, showed that an animal primarily subjected to a subtotal pancreatectomy, and subsequently to a subtotal hypophysectomy, ultimately acquired an increase of tolerance for glucose over that which existed before either operation was done. This would seem to indicate that an insulin deficiency with hyperglycemia may be more than compensated for by the production of a secondary hypophysial deficiency. In support of these experimental results are the observations of Fry [31] who examined the pituitary glands of eight diabetic patients and described certain changes in the hypophysis, such as an increase in eosinophilic cells and excess of colloid, which were interpreted as evidencing hyperactivity.

The experiences of others to the contrary are more in accord with what our present knowledge of the subject would lead us to expect—namely, retrogressive rather than hypertrophic changes in the hypophysial anterior lobe. Thus Kraus [32] examined the hypophysis in twenty-three cases of diabetes; such changes as were found to exist were limited to the eosinophilic elements of the anterior lobe and were thought to be degenerative. Believing that underactivity of the anterior lobe produces an increase in carbohydrate tolerance, he explained the changes on the basis of a self-regulatory and interglandular carbohydrate mechanism. Vernon [33] also found degenerative changes in the hypophysis in three out of six diabetic patients.

We may therefore conclude from the several, though in part contradictory observations mentioned in this section, that the pancreas and probably its islet tissue exerts a reciprocal effect on the hypophysis; that both pancreatic islets and hypophysis have some influence on sugar

31. Fry, H. J. B.: The Pituitary Gland in Diabetes Mellitus and Disorders of Glands of Internal Secretion, Quart. J. Med. **8**:278, 1915.

32. Kraus, E. J.: Hypophyse und Diabetes Mellitus, Virchows Arch. f. path. Anat. **228**:68, 1920.

33. Vernon, O.: Ueber die Bedeutung der Hypophyse in der Pathogenese des Diabetes Mellitus, Centralbl. f. allg. Pathol. u. path. Anat. **31**:521, 1921.

metabolism; that insulin serves to affect favorably both acromegalic and pancreatic forms of the disease; and that a hypophysectomy may offset experimentally produced pancreatic diabetes. We may now turn to a consideration of the subject of the glycosurias from the primary standpoint of the hypophysis.

RELATION OF THE HYPOPHYSIS TO THE GLYCOSURIAS

The first evidence that prompts us to expect such a relationship is, as noted at the outset, the frequency of glycosuria, variously estimated from 25 per cent to 40 per cent in acromegalic patients. Since the conclusions, based largely on clinical and circumstantial evidence, that acromegaly is an expression of hyperfunction of the pituitary have been conclusively supported by the experiments of H. M. Evans and his co-workers,[34] the hyperglycemia and glycosuria found in association with acromegaly, if at all related to the hypophysis, must be a result of its overactivity; and what is more, they must be associated with oversecretion of the acidophilic cells of the pars anterior.

On an experimental basis little has as yet been done to substantiate this statement, which rests largely on clinicopathologic deductions. Borchardt [7] made parenteral injections of saline extracts of fresh equine pituitary glands into thirty rabbits with a resulting glycosuria in twenty-three and a hyperglycemia in two of the animals. The effect of similar injections in dogs was less striking. In his experiments, unfortunately, the posterior lobe was included in the extract.

Miller and Lewis [35] injected pituitary extracts into thirty small dogs, half of them given anterior lobe and half posterior lobe extracts. Glycosuria occurred in three animals, and two of these had received anterior lobe injections.

Goetsch, Cushing and Jacobson [17] in their studies on the sugar tolerance of hypophysectomized animals observed that the high tolerance for glucose shown by some of their animals, and found to be accompanied by hypoglycemia, could be overcome and glycosuria produced by the hypodermic injection of anterior as well as of posterior lobe extracts. Since the discovery of insulin, Houssay and Magenta [36] have reported that hypophysectomized dogs which recover with symptoms of glandular insufficiency are much more sensitive to the effects of the injection of insulin than normal animals, and are easily rendered hypoglycemic.

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34. Evans, H. M.: The Function of the Anterior Hypophysis, Harvey Lecture Series, Philadelphia, 1923-1924, p. 212.

35. Miller, J. L., and Lewis, D.: The Frequency of Experimental Glycosuria Following Injections of Extracts of the Hypophysis, Arch. Int. Med. **9**:601 (May) 1912.

36. Houssay, B. A., and Magenta, M. A.: Sensibilidad en los perros hipofisoprivos a la insulin, Rev. Asoc. méd. argent. (Soc. de Biol.) **37**:389, 1924; Compt. rent. Soc. de biol. **92**:822, 1925.

These corroboratory observations would lead one to suppose that in the opposed condition of experimental hyperpituitarism the animals would be much less sensitive. So far as we are aware, however, no studies have as yet been made on the blood or urine of Evans' rats or of other animals given injections over long periods with active anterior lobe extract. We may assume that they will show hyperglycemia.

On clinical grounds attention may be called to the frequent occurrence of glycosuria in pregnancy (11.8 per cent according to Reichenstein), during which, as first demonstrated by Erdheim and Stumme,[37] the hypophysial pars anterior enlarges and takes on additional activity; indeed repeated pregnancies may be the forerunner of acromegaly, as is well known. Attention may be called also to the not infrequent appearance of glycosuria in the period of rapid growth associated with adolescence, which in all likelihood is an expression of the same pituitary activity responsible for the rapid increment of growth in acromegaly. That the combination may at times be puzzling to clinicians is exemplified by a case recently referred to the senior author by Dr. E. P. Joslin. The story follows.

Richard M. is a boy 8 years of age who looks easily 14. He is 53 inches tall (5 inches over the average for his age) and weighs 79 pounds (average for his age, 54 pounds). He has been in perfect health, is an exceptional student and the leader in his school. He was accidentally found to have 5 per cent sugar in his urine. This disappeared under treatment with insulin. The question arises whether this is primarily pancreatic or primarily hypophysial diabetes. The roentgen ray shows a normal sella.

Another question which might be raised by such a case is whether the recognized peak of diabetes in childhood at about 14 years is in any way related to a period of unusual activity of the anterior hypophysis. On the contrary, it is not inconceivable that the pancreatic diabetes of childhood may secondarily stimulate the anterior hypophysis, which would be in accordance with Fry's observations.[38]

The injection of such a case into this discussion may appear to be remote from the subject of acromegaly but, after all, the hormone is probably the same whether gigantism or acromegaly or mere overgrowth is produced. Experience has taught us that pituitary insufficiency whether clinical or experimental is accompanied by a high sugar tolerance, or expressed in the terms of Houssay's experiments, just mentioned, in leaving the patient more sensitive to insulin. We are inclined to believe too, on theoretical grounds as well as on the grounds of experience, that patients with hyperpituitarism (acromegaly) are on the other hand less sensitive to insulin than normal persons.

37. Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse, Beitr. z. Path. Anat. u. z. allg. Pathol. **46**:1, 1909.

38. Dr. Joslin informs us that a study of 100 diabetic children shows them to average 2.7 inches above the standard height at the onset of their disease.

The Counteraction of Pituitary Extracts and Insulin.—The antagonism of these two substances was first pointed out in an important article by J. H. Burn.[39] The observation has been supported by the experience of the clinic. In three of our patients with acromegalic diabetes who had been shown to respond normally to insulin, 20 units of insulin combined with 1 cc. of solution of pituitary, U. S. P. (the brand used was pituitrin, P. D. & Co.) were injected. The results are given in table 2 and show that the expected fall in blood sugar at the end of a two hour period had not occurred.

These figures confirm Burn's interesting disclosure that the two substances are mutually antagonistic. It was also shown by Burn that pituitary extract would counteract the hypoglycemic reaction in animals of over dosage with insulin, and this has proved of benefit in clinical cases. One would expect, therefore, that the injection of pituitary extract alone would greatly increase the blood sugar. The test was made on case 2 cited in table 2, and though a definite increase in blood

TABLE 2.—*Blood Sugar*

	Case 1	Case 2	Case 3
Fasting	0.33%	0.13%	0.15%
	20 units insulin + 1 cc. solution of pituitary subcutaneously	20 units insulin + 1 cc. solution of pituitary subcutaneously	20 units insulin + 1 cc. solution of pituitary subcutaneously
After 2 hours	0.32	0.14	0.142
After 4 hours	0.30	0.12	0.112

sugar was observed four hours after the injection, it was less than we had expected. This is a matter which deserves further study, but the single clinical observation recalls the experiences of Burn, who states that posterior lobe extract when given by itself to his experimental animals failed to produce a rise in blood sugar sufficient to explain the inhibition of the action of insulin when the two substances were injected together.

Ellis,[40] in an interesting report of a case in which the diabetes of acromegaly had disappeared after a successful hypophysectomy, theorizes on the cause of the glycosuria and suggests that it is due to an increased activity probably of the pars intermedia, whose extract, like that of the pars nervosa, inhibits the normal action of insulin on carbohydrate metabolism. He based this hypothesis on the statement of H. M. Turnbull that acromegalic adenomas arise from this intermediate portion of the gland, whereas the view generally accepted is that they arise

39. Burn, J. H.: The Modification of the Action of Insulin by Pituitary Extract and Other Substances, J. Physiol. **57**:318, 1923.

40. Ellis, A. W. M.: Hyperglycaemia and Glycosuria in Acromegaly with Pathological Report by Prof. H. M. Turnbull, Lancet **1**:1200, 1924.

from the acidophilic cells of the anterior lobe. Other than for this apparent point of discord we find ourselves in agreement with the author's interpretation of his case.

This mention of the seat of origin of the chromophile adenomas brings up another question for which as yet there is no reasonable answer. Why should posterior lobe extracts be those to counteract insulin when, so far as is known, hyperpituitarism, which alone of hypophysial diseases provokes glycosuria, is an anterior lobe disorder? This is but one of the many apparent contradictions met with in the study of pituitary function, the key to which is not as yet in our hands.

As a matter of fact, we know little about the source or nature of the actual substance found in the posterior lobe, familiar as we may be with its many functions. Whether the cells of the pars anterior or pars intermedia play any part in the formation of the active principle of the posterior lobe is unknown, though histologic preparations of the hypophysis in certain conditions of disease suggest that they may; and though we are loath to lay any particular stress on the finding, it may be stated that in two of the acromegalic hypophyses in our collection the posterior lobe had become abundantly invaded by epithelial cells. It possibly may come to be shown that the posterior and anterior lobes have interdependent rather than the quite separate functions generally ascribed to them.

One thing obviously remains to be done, namely, to test the counter-effects on insulin of an active anterior lobe extract simultaneously injected. This has been tried by Burn with negative results in animals, and unfortunately no substance of this sort sufficiently free from protein and infectious material is yet available which can be used with safety on the human subject. We would be inclined to assume that an active anterior lobe substance might be even more directly antagonistic to insulin than the extract of the posterior lobe, but it may not prove to be so.

SUGAR TOLERANCE TESTS ON ACROMEGALIC PATIENTS WITHOUT GLYCOSURIA

In addition to the surprisingly high percentage of acromegalic patients that show either glycosuria or frank diabetes, we have observed that acromegalic patients who show no sugar in the urine may have a subnormal capacity to dispose of carbohydrates when given intravenously. In order to eliminate the variability in the degree of absorption of sugars given by the oral method, the glucose tolerance test that was finally adopted by us for the purpose of this study was as follows:

Early in the morning while fasting, the patient was weighed and a specimen of urine voided. Blood was taken for a fasting blood sugar determination and

immediately thereafter a purified 20-25 per cent glucose solution in normal saline was injected intravenously, the period of injection lasting from fifteen to twenty minutes, depending on the quantity used. The amount was determined by the patient's body weight, 0.5 Gm. of glucose per kilogram being used. Blood was then removed for sugar tests at one-half, one and two hour intervals following the injection. The urine sugar was quantitated at the end of the two hours.

The blood sugar curves obtained in ten tests of this sort performed on nine patients with acromegaly, two of whom had a mild degree of diabetes mellitus are shown in chart 2. It will be seen from this graph that all the curves rise above the normal one, and, with a single exception, remain higher than the normal throughout the period of examination. Eliminating from consideration the two patients with clinical diabetes, in whom a decreased tolerance for glucose would naturally be expected, it would appear that a tendency exists among all the other seven toward a similar intolerance.

The literature contains few examples of tests of this sort made on patients under similar circumstances, namely, intravenous injection of glucose into acromegalic patients without diabetes. Perhaps the first sugar tolerance test to be carried out on such a patient, the oral method having been used, was by Strümpell [41] who found glycosuria in his patient after the ingestion of only 100 Gm. of glucose.

Wilder and Sansum [42] report on five pituitary cases—two acromegalic cases, one case of "suspected gigantism" and two with "dyspituitarism showing Fröhlich's syndrome." Their tests were carried out by the use of apparatus which permitted the continuous injection of a given percentage of glucose at a uniform rate, and they took the tolerance level to be that just above which sugar appears in the urine. In a series of normal persons they established the fact that "glucose injected at the rate of 0.8 Gm. per kilogram of body weight per hour caused no glycosuria, but in each case sugar appeared in the urine when the injection rate was 0.9 Gm. per kilogram per hour." In their pituitary cases, on the other hand, they found that, "three showed a bare trace of sugar in the urine after the injection of 0.8 Gm. per kilogram per hour, and all gave a definite glycosuria after receiving 0.9 Gm. per kilogram per hour." Unfortunately, they fail to state, what is of greatest interest from our point of view, namely, which three of their five cases showed a lowered tolerance; but in the light of our observations the three concerned must have been the two cases of acromegaly and the case of "suspected gigantism."

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41. Strümpell, A.: Ein Beitrag zur Pathologie und pathologische Anatomie der Akromegalie, Ztschr. f. Nervenheilk **11**:51, 1897.

42. Wilder, R. M., and Sansum, W. D.: d-Glucose Tolerance in Health and Disease, Arch. Int. Med. **19**:311 (Feb.) 1917.

Major [43] included one nondiabetic acromegalic patient in his studies on sugar tolerance, but his tests also were by means of oral administration of glucose, although followed by blood sugar determinations. He believed that his patient showed an increased sugar tolerance. His test, however, not only is open to the objection applicable to all tests carried out by the oral method of administration, but he also delayed one hour after the ingestion of the glucose before taking the first blood sugar reading, thus, as pointed out by Sachs and MacDonald,[44] missing the initial rise determinable at the end of half an hour. His patient, moreover, may have chanced to be in the stage of inactive acromegaly.

Two papers pertaining to the subject at hand have recently been written by H. J. John.[45] The earlier paper, which is concerned with the spontaneous disappearance of diabetes, contains two case reports, one of a typical acromegalic patient with diabetes who had failed previously to be benefited by insulin. After a renewed and more vigorous insulin regimen, the patient became sugar-free, and three months later a sugar tolerance test gave, to the author's "astonishment," a normal curve. The case was regarded as one of diabetes in which the acromegaly was merely coincidental. It, however, is included in John's second paper which deals more specifically with acromegalic diabetes, of which he reports two further examples. In one of them, briefly recorded as a case of acromegaly without glycosuria, it is nevertheless stated that "there was slight leaning toward impairment of carbohydrate function," as shown by a sugar tolerance test.

All this is quite in accord with our own views, but we find ourselves at variance with this author in his statement that 12 per cent of the patients in the Cleveland Clinic with *hypo*pituitarism had more or less marked diabetes—in other words, as large a percentage of diabetic patients as is usually seen in *hyper*pituitarism. This is so contrary to the observations of others that one is led to query what conditions may have been classified as hypopituitarism. In the entire series of 168 patients from the Peter Bent Brigham Hospital with histologically verified pituitary adenomas recorded as "chromophobe," only four prove to have shown even a transient glycosuria. The tissues of these four cases have since been reinvestigated with special stains, and two of them at least are distinctly acidophilic in type. We are inclined to feel therefore that the presence of glycosuria or hyperglycemia with

43. Major, R. H.: Studies on Sugar Tolerance, Bull. Johns Hopkins Hosp. **34**:21, 1923.

44. Sachs, E., and MacDonald, M. E.: Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions, with a Review of Literature, Tr. Am. Neurol. A., 1924, pp. 129-162.

45. John, H. J.: Spontaneous Disappearance of Diabetes, J. A. M. A. **85**: 1629-1631 (Nov. 21) 1925; The Possible Relationship Between Acromegaly and Diabetes, Arch. Int. Med. **37**:489 (April) 1926.

pituitary disease in the vast majority of cases implies hyperpituitarism, even though the clinical evidence of overgrowth may scarcely suffice to justify the term acromegaly as Pierre Marie employed it.

This is a matter which we hope to consider at another time and place. It is safe to say, with the data at hand, that the majority of patients with acromegaly have difficulty in metabolizing carbohydrates, and that even in the absence of melituria, they tend to show a relative hyperglycemia in the active stages of the disease.

THE COURSE AND PROGNOSIS OF ACROMEGALIC DIABETES

The belief seems to be widespread among those who have written about diabetes that the usual form of the disease differs in no respect from that which happens to be associated with acromegaly. This statement is explicitly made by John,[46] for example, who adds that a hypophysectomy has never been known to cure a patient of pituitary diabetes.

To these two questions we may now pass: Does the diabetes of acromegaly differ from ordinary diabetes? Do hypophysectomies for the acidophilic adenomas of the disease serve to influence favorably the disturbed carbohydrate metabolism whether or not they may be regarded as effecting a cure?

The convictions of those best informed regarding the course and prognosis of ordinary diabetes may be fairly assumed to be contained in the statement of Futcher in the last edition (vol. 2, 1926, p. 53) of Osler's "Modern Medicine," when he says:

> Generally speaking, the later in life the symptoms first manifest themselves, the better is the prognosis. The majority of cases after middle life run a chronic course, and it is not very uncommon to see stout, elderly individuals in whom the disease has lasted ten to fifteen years. Cases with hereditary influences are the most favorable. Once the disease is well established, it is seldom, if ever, that a permanent cure is effected.

The introduction and perfection in the therapeutic use of insulin had raised the hope that means not only of alleviating but possibly of curing the diabetes had been found. We may still cling to the hope, for we do not yet know all that insulin may accomplish, but Harrison [47] concludes his careful investigation of the subject with the statement that "no case of diabetes mellitus has yet been published in which it was possible eventually to stop the insulin entirely and to allow an absolutely unrestricted diet without the return of hyperglycemia."

The contrast between these well established opinions and the course observed not only occasionally but frequently in the diabetes associated

46. John, H. J.: The Possible Relationship between Acromegaly and Diabetes, Arch. Int. Med. **37**:489 (April) 1926.

47. Harrison, G. A.: Can Insulin Produce Even a Partial Cure in Human Diabetes Mellitus? Quart. J. Med. **19**:223, 1926.

with acromegaly is most striking. Long before Opie's discovery [48] of the relation between diabetes and the islands of Langerhans, observers were impressed by the bizarre fashion in which the glycosuria in cases of acromegaly would appear and disappear without relation to dietary restrictions. The point which was particularly emphasized by von Noorden [49] has been recognized by other writers on the subject, and is in full agreement with our many personal observations.

There is no difficulty in accounting for this fluctuating character of the acromegalic glycosurias. Hyperpituitarism as expressed by acromegaly is not a steadily progressive disorder and behaves in this respect much as does hyperthyroidism. There are distinct waves of what the patient recognizes as more or less intense periods of "acromegalism". Some patients with pronounced acromegaly go through a long life little troubled by these symptoms; others are continually more or less miserable from the toxic effects of the disease which may at times so closely resemble those of thyreotoxicosis that they may be subjected to thyroid extirpations on the mistaken idea that the goiter, which may be present, is the primary cause of the malady rather than a secondary effect. Still other patients may never have more than a single primary wave of transient hyperpituitarism, and such evidences of overgrowth as may have been occasioned remain barely discernible. Indeed, the acidophilic adenoma which is unquestionably the underlying lesion may become completely degenerated and cystic, just as may a thyro-adenoma, and signs of actual pituitary insufficiency come to be superimposed on the relics of a once active acromegaly.

These clinicopathologic aspects of the disease appear to be scarcely appreciated or borne in mind by those who have, from a biochemic or physiologic standpoint, made reports on an isolated case or two. But with these peculiarities of the malady clearly before us, we may more easily appreciate how it happens that acromegalic patients may show waves of melituria, even periods which justify the designation of actual diabetes and yet spontaneously recover from them, irrespective of any dietary restrictions or treatment by insulin. One of our patients, an intelligent and observant woman, who had a transphenoidal operation twelve years ago with marked relief from her pressure symptoms, continues nevertheless to have recurrent periods of "acromegalism"; and with each wave of the process, which is signalized by a sense of exhaustion, she becomes temporarily highly glycosuric.

Without a long series of cases studied with these characteristic periodicities of the malady in mind, it is obvious that the effects of an

48. Opie, E.: Disease of the Pancreas; Its Cause and Nature, Philadelphia, J. B. Lippincott Company, 1903.

49. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, ed. 6, Berlin, 1912.

operation in itself may be most difficult to determine. For a crucial test not only must the operation have been a radical one and performed on a patient with pronounced melituria, but the patient must also be kept under observation for a long time and have repeated determinations of urine and blood sugar under varying conditions of activity and diet. These opportunities are rare.

In an earlier paper in the series [2] we have given in some detail the history of an acromegalic patient whose long-standing diabetes had disappeared, subsequent to, though not convincingly because of, a hypophysectomy. He at least had become sugar-free, with no dietary restrictions, a year later, when he died from cardiac failure with generalized anasarca. To illustrate further the difficulties of determining what credit if any may be ascribed to an operation rather than to other causes, when a patient who has once had melituria subsequently remains sugar-free on an unrestricted diet, the following case may be cited:

Advanced acromegaly of about seven years' duration. Symptoms of diabetes of about twelve months. Control of diabetes by insulin. Transsphenoidal operation. No return of glycosuria for six months on an unrestricted diet.

C. S., an unmarried Greek man, aged 31, was referred to us by the Veterans' Bureau on *Jan. 29, 1929.* His illness began about 1919, with severe headaches, weakness, accession of weight, profuse sweats, increase in size of hands and feet, and diminution of sexual power.

He was a typical acromegalic with large extremities and features, mandibular prognathism, spaced teeth, hypertrichosis, hyperhidrosis, a ballooned sella, primary atrophy and beginning bitemporal hemianopia.

According to the clinical notes accompanying the case, the urine on one occasion in September, 1914, had shown a trace of sugar. The patient, however, gave a history of increased thirst and polyuria for a period of only about a year previous to admission.

On the day following his entry to the hospital his urine showed 5.5 per cent sugar, and his blood sugar was 0.25 per cent. While on an unrestricted diet, and in spite of his large appetite, his blood sugar in the course of three days dropped to 0.15 per cent and his urine sugar to 1.8 per cent. These levels were maintained for the succeeding two weeks From *February 14* to *February 25* he was given insulin in increasing doses. Not until he had received twenty units twice a day did he become practically sugar-free. Insulin was then discontinued, and although he subsequently showed little more than a trace of sugar in the urine, he nevertheless continued to have a slight hyperglycemia.

Between the dates of *February 28* and *March 3* he had a severe tonsillitis with a temperature of 102 F. without affecting his condition; his blood sugar taken on one of these days was nearly 0.2 per cent although with only a trace of sugar in the urine.

He was followed through the month of March without any further change. On *March 12,* when his blood sugar showed 0.13 per cent and he had a trace of glycosuria, he was given 20 units of insulin coincidentally with 1 cc. of surgical pituitrin. This caused a slight rise in his blood sugar percentage (table 2, case 3) rather than the fall (table 1, case 3) which occurred under insulin alone. On *March 30* he was given an intravenous sugar tolerance test with the result recorded on chart 1, case 1. During the first three weeks in April there was only an occasional trace of sugar in his urine, but his blood sugar on repeated tests remained slightly elevated, averaging 0.15 per cent.

On *April 22, 1926,* under ether, the usual transsphenoidal operation was performed with the partial removal of a chromophile adenoma. The procedure, owing to anatomic conditions, was difficult and prolonged and was not as radical as it might otherwise have been.

In spite of this long operation his first postoperative specimen of urine showed no sugar, nor was there any increase in the percentage of blood sugar. On the contrary, his blood sugar showed on successive tests a moderate fall below the previous average of 0.15 per cent. On *May 13* he was given his first postoperative intravenous sugar tolerance test (chart 1, case 1) when his fasting blood showed 0.12 per cent, and the curve was considerably lower than his preoperative curve.

From the time of his operation until his discharge on *May 17,* his urine remained sugar-free. Meanwhile he not only had a marked subjective improvement in his pressure symptoms, but there was a definite objective subsidence in his acromegalic "myxedema." At the present time, six months later, he remains well, and according to reports from the Veterans' Bureau in New York there has been no glycosuria, though the blood sugar when last tested showed 200 mg. per one hundred cubic centimeters of blood.

Here, then, was a man retained in the hospital for purposes of study over a long period, who at entrance showed a 5.5 per cent of glycosuria with a total twenty-four hour output of 104 Gm. of sugar, and who subsequently became sugar-free even though his hyperglycemia persisted. It can hardly be claimed that the comparatively unsatisfactory operation in this case and the disappearance of his glycosuria were anything more than coincidental, and the case is given largely to show the difficulties of interpretation which attend these studies.

There have been other cases of acromegaly in the series with serious grades of persistent diabetes with which the partial and conservatively conducted hypophysectomy has had no definite effect on the disturbed sugar metabolism. What is more, in one or two of these intractable cases it has been found particularly difficult to get the disorder under even partial control by insulin. Acromegalic patients often have an inordinate appetite even when they are not glycosuric. Their polyphagia often completely dominates them, and since they are not prone to lose weight and often feel more miserable from the effects of their "acromegalism" when their food is restricted, they look on their diabetes as a secondary consideration and treat the admonitions of the physician with indifference.

The following case will illustrate this point and at the same time will show not only that a severe diabetes may be surprisingly well borne by an acromegalic patient but also how relatively intractable it may be to insulin before an operation.

Acromegalic male with diabetes of six years' duration. Diabetes most recalcitrant to insulin before hypophysectomy; easily controlled subsequently.

An Indiana farmer, aged 41, was admitted to the hospital on *Nov. 25, 1925.* He showed advanced acromegaly, the changes in his features and extremities having been first noted about ten years previously. Six years before admission, following an attack of influenza, he began to have severe bitemporal headaches, increase in thirst and polyuria. Glycosuria was discovered at that time, and

dietary treatment instituted. He adhered to the restrictions for twenty months, felt well enough meanwhile, but at times the urine showed a good deal of sugar. This so discouraged him that he abandoned the diet and yet in spite of a ravenous appetite which was fully satisfied he continued at times to be sugar-free and at others to show large quantities of sugar. He meanwhile was engaged in heavy manual labor, and for the month before he came under observation had been pitching hay and following a plough.

At the time of admission, aside from the marked acromegalic overgrowth, the primary optic atrophy, typical defects of the visual field, and the large sella turcica demonstrated by roentgen-ray examination, he showed a blood sugar of 0.28 per cent, glycosuria of from 5 to 6 per cent with a daily excretion of from 125 to 150 Gm. of sugar. No acetone bodies were at any time detected in the urine.

After a week of preliminary observation he continued to show from 5 to 7 per cent of urine-sugar without ketosis on a full diet. He was then put on a diet restricted only in the sense that bread and sugar were limited, and an insulin regimen averaging 15 units three times a day. His fluid intake and output immediately became reduced from 3,500, 4,000 to around 2,000 cc. daily, and his glycosuria to from 1 to 2 per cent, but his blood sugar continued at 0.25 per cent. His basal metabolic rate, which was + 38 per cent before the use of insulin, had dropped to + 14 per cent after five days' treatment. At the end of this period a return to an unrestricted diet without insulin promptly resulted in an elevation of the glycosuria and fluid-exchange and a rise in the basal metabolic rate to + 22 per cent. A week later insulin with dietary restriction was resumed, and it was found that 25 units three times a day for five days did not eliminate his glycosuria, and the amount was carried up to 40 units three times a day without rendering the urine sugar-free. He was operated on the following day.

Operation.—Dec. 23, 1925. By the usual transsphenoidal operation under ether anesthesia a generous portion of his pituitary adenoma was removed. He seemed little disturbed by the operative procedure, although his blood sugar taken at the end of the operation had risen to 0.36 per cent. Five hours later it was 0.23 per cent.

He made an uncomplicated recovery from the operation, following which, without insulin and on an unrestricted diet, he showed a marked polyuria and a urinary sugar excretion at times of over 300 Gm., but there were never any signs of acidosis.

On *Jan. 18, 1926*, he was put on a weighed diet of 3,000 calories (carbohydrate 100, protein 125, fat 250) with 30 units of insulin twice daily. He continued, however, to show at least a trace of sugar until his discharge on January 26. The blood sugar had remained in the neighborhood of 0.25 per cent until his last day in the hospital when it had suddenly dropped to 0.13 per cent, and for the first time since his admission his urine failed to show sugar. He has since continued on an insulin regimen of 25 units twice a day, has resumed his active life, and though he shows great variability in his glycosuria, his physician reports his condition to be greatly improved.

What particularly struck Dr. Fitz, who collaborated with us in the conduct of the case, was the fact that a man with diabetes of six years' standing who had largely ignored it for over four years and yielded to the dictates of a ravenous appetite showed no acetone bodies in the urine, and who, in spite of a complaint of weakness, had engaged in heavy labor up to the time of his admission. He responded to insulin by a decrease in sugar output, but his blood sugar remained little affected, and it was not until after his operation that an insulin regimen

in amounts which previously had been ineffective finally caused his glycosuria to disappear and reduced his hyperglycemia. How much if any credit for this may be given to the partial hypophysectomy is difficult to say. Certainly the changes were not immediate nor were they striking. Even so, the hypophysis is not necessarily ruled out as the important factor, for insufficient tissue may have been removed to cause a prompt effect, or the pancreatic islets may have been seriously damaged by his long-standing and neglected diabetes.

Another similarly intractable case in the series in which the diabetes remained unmodified after a possibly insufficient removal of the adenoma has been kindly studied for us by Dr. E. P. Joslin. This patient suffers from intolerable acromegalic headaches and is quite indifferent to her outspoken diabetes of about two years' duration which has been notably resistant to insulin in our hands as well as in the hands of others. In this case also though Dr. Joslin found her melituria to be influenced by insulin, he found also that her blood sugar did not seem to be correspondingly modified but remained surprisingly high when compared with the amount of sugar in the urine. This patient also feels much better when on an unrestricted diet, frets under an insulin regimen, and seems to do just as well without it.

Another point that might be mentioned is that patients with acromegaly and diabetes may nevertheless pass safely through severe infections and serious surgical operations and ultimately succumb to some cause unassociated with the diabetes. There are several examples of this in our series which might be detailed were it not that the literature contains many reports of the kind, and the added recital herein of others would unduly prolong this discussion.

It is undoubtedly true, on the other hand, that many acromegalic patients with diabetes end their days after the expected fashion of patients afflicted with the latter disease alone, that is, by coma supervening on a pneumonia or some other infection. Froment [50] collected twelve examples of this from the literature; one of John's [48] patients met with a similar end, and undoubtedly a record of many others might be found. Thus one of the twelve patients with acromegalic diabetes in the series under review died in coma as recorded in detail in a previous paper,[2] the postmortem examination failing to show any recognizable abnormalities in the pancreas.

It is evident from a comparison of the causes of death of acromegalic patients with diabetes with the causes of death of patients with pancreatic diabetes as cited by Root and Warren [22] from Joslin's clinic that the former are more often unrelated to the disturbance of sugar metabolism. This, after all, is what would be expected in view of the

50. Froment, J.: Rapport de réunion Société de Neurologie, Rev. neurol. **29**:663, 1922.

many added complications which the acromegaly and its tumor would incur. However, in spite of this the average survival period after the appearance of the glycosuria proves to be about the same in both groups, namely, from ten to eleven years,[51] which would indicate a better prognosis for the diabetes of acromegaly considered by itself.

Associated with the acromegalic diabetes, moreover, in many instances is a high basal metabolic rate and this constitutes another point of difference from ordinary diabetes in which, as is well known, the basal metabolic rate is not markedly affected whether the patient is insulinized or not. This we have touched on in a preceding paper dealing with the metabolic rate in the disease.[3] The complexity of the problem therefore, owing to the secondary effects of the hyperpituitarism on the thyroid as well as on the pancreatic islets is undeniably considerable.

THE EFFECT OF HYPOPHYSIAL OPERATIONS ON SUGAR TOLERANCE IN ACROMEGALY

The argument has been raised by those who regard diabetes mellitus as the same disease whether or not it is accompanied by acromegaly, that a hypophysectomy has never been known to bring about a cure of the diabetes. This is a matter which perhaps requires some explanation by the surgeon.

It scarcely needs to be emphasized that surgery of the hypophysis in general is still in its infancy; that the operations which are gradually becoming perfected have in the past been almost wholly confined to the single purpose of preserving vision by relieving the chiasm from the effects of pressure by the adenoma; that the adenomas so attacked are far more often accompanied by the clinical aspects of hypopituitarism, a condition the reverse of acromegaly, than by acromegaly itself.

Consequently, operations on acromegalic patients with this primary purpose in view, of lessening the pressure effects of a large adenoma which have at the same time served to lessen the general effects of the hyperpituitarism, have been few. What is more, the number of operations on acromegalic patients with diabetes in which both preoperative and postoperative dependable determinations of blood sugar have been made almost reach the vanishing point.

Hence when one speaks of "curing" the diabetes of acromegaly by a hypophysectomy, we have as yet not much to go on. In dealing with such a complex subject and one with so many facets as the treatment of hyperpituitarism, regardless of its secondary complications, progress comes slowly. The problem is technically far more difficult than the

51. In the days before insulin the average survival period of patients with pancreatic diabetes was variously estimated at from four (Fitz and Murphy) to six (Joslin) years.

operative treatment of, for example, hyperthyroidism for which a subtotal thyroidectomy has become a fairly well standardized procedure.

Possibly the most convincing case in the literature is that reported by Ellis,[40] to which reference has already been made:

A woman, aged 42, with acromegaly of ten years' standing and diabetic symptoms of possibly eight months' duration, showed 0.43 per cent blood sugar and 10 per cent glycosuria with acetone bodies in large quantities. After three days' fasting she became sugar-free and was maintained so by a limited diet for three weeks. Then by a long operative procedure under ether a partial extirpation of the pituitary growth by the transfrontal route was performed. She showed only a trace of glycosuria postoperatively, and in spite of increasing laxity of diet had remained free from glycosuria up to the time of the report three years later, although sugar tolerance tests showed a relative hyperglycemia.

In this case Mr. Walton, the surgeon, from all accounts carried out a more radical extirpation of the hypophysial adenoma than is usually accomplished, though the pathologist's description of the tissues described them as fragmentary. However this may be, the acromegalism so far as the diabetes was an expression of its activity, appears to have been definitely checked for a period of thirty-six months when the case was reported.

In the 100 examples of outspoken acromegaly made the basis of this series of papers, twenty-five of them, as stated, showed various grades of melituria, and of these patients fourteen have been subjected to hypophysial operations usually because of symptoms of tumor and most of them in days gone by without any particularly detailed observations on the degree and course of the existent glycosuria or diabetes. Since our interest in the matter has become revived, we have observed an immediate postoperative cessation of a preexisting glycosuria in only one case, a brief account of which follows:

Acromegaly of moderate degree. Transsphenoidal operation with radical removal of small adenoma. Immediate cessation of preexisting glycosuria.

A married Italian woman, 22 years of age, first came under observation on *Dec. 17, 1925*, with the chief complaint of headaches. These were of two years' standing and had set in during the course of her first and only pregnancy. The headaches during this period had become increasingly severe. Meanwhile her hands and feet had enlarged; her features had become coarse and heavy; a growth of hair had appeared on the lip and chin with general hypertrichosis; and there had been a notable increase in weight. There was marked sweating and nervousness. She had a small sella and no disturbance of vision. There was no glycosuria and the blood sugar showed 0.13 per cent. She was discharged.

She reentered the hospital on *Aug. 27, 1926*, owing to great increase in her cephalalgia and in her general symptoms of acromegalism. Her urine on admission showed no sugar, but on *September 2* she was found to have a glycosuria amounting to 0.7 per cent (9.5 Gm.). Without dietary restrictions the urine continued to hold about this percentage of sugar until the operation. On one occasion, *September 6*, she showed diacetic acid which may possibly have been due to the acetylsalicylic acid she was taking for her headaches. She

had an increased basal metabolic rate of + 25 per cent and was put on Lugol's solution on *September 2*, 5 drops three times a day, which was continued for fourteen days without appreciably affecting the rate. Her blood sugar on *September 10* was 0.14 per cent.

On *September 20, 1926,* under ether anesthesia she was operated on by the usual transsphenoidal route with the purpose of radically cleaning out her adenoma even though she showed no local symptoms other than her severe acromegalic headaches. The operation, which was easily conducted, was satisfactory in all respects; the tissue showed an acidophilic adenoma. She made an excellent recovery with immediate cessation of her headaches and early subsidence of her pituitary myxedema.

Her blood at the termination of the operation on *September 20* showed a sugar content of 0.24 per cent; three days later, on *September 24,* 0.12 per cent; on *September 28,* 0.11 per cent, and on *October 1,* 0.09 per cent.

There was an immediate postoperative disappearance of her glycosuria, not a trace of sugar having been observed at any subsequent examination during her hospital sojourn. She was discharged on *October 20.*

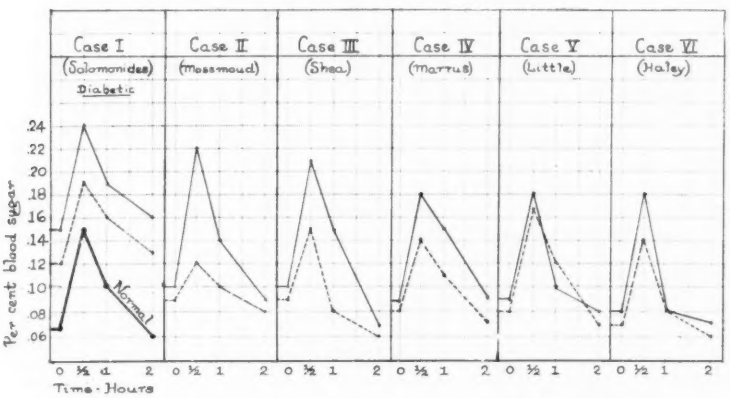

Chart 1.—Blood sugar tolerance curves in six cases of acromegaly before (continuous) and after (broken lines) operation, showing a postoperative lowering in the blood sugar levels. The heavy lines represent a normal curve for comparison.

Although such a case as this is suggestive, it can hardly be spoken of as a "cure" of acromegalic diabetes, for when the patient came under observation, there may have been merely a wave of melituria with which the operation happened to coincide. Her postoperative fall in blood sugar, however, is something to which we desire to call especial attention, for it permits us to tell, in closing, another story which is perhaps more convincing. This concerns the effect of the hypophysectomy on the hyperglycemia of acromegalic patients in the absence of any history of glycosuria. The lowering of the existing hyperglycemia by the partial removal of an acromegalic adenoma under these circumstances indicates what may come to be accomplished in the more severe grades of disturbed sugar metabolism when more radical operations are devel-

oped and successfully undertaken. For with the knowledge that hypopituitarism is associated with a relative hypoglycemia and assuming the existence of hyperpituitarism with adenomatous changes in every case of acromegaly, at least during the active stages of the disease, it would seem justifiable to expect an improvement in the patient's impaired carbohydrate tolerance by a partial operative removal of the hyperplastic tissue. In six of the nine patients mentioned in the section on sugar tolerance whose blood was studied both before and after operation, we have observed such a response.

In chart 1 the curves of sugar determinations in these cases are separately shown, those taken before operation in continuous and those

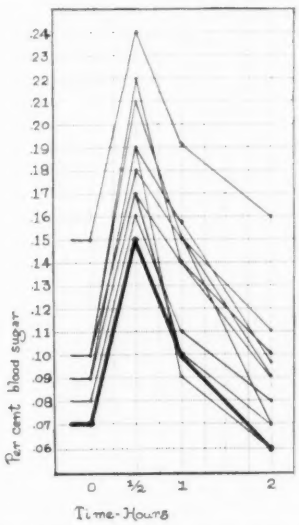

Chart 2.—Preoperative blood sugar tolerance curves in six cases, and four curves in three additional cases in which operation was not performed, all superimposed, showing invariable decrease in sugar tolerance. Normal curve in heavy lines is for comparison.

taken after operation in broken lines. It is evident at a glance that in all but two of the cases, in which the changes are insignificant, there has occurred a distinct improvement on the part of each patient to handle glucose after the partial hypophysectomy. In chart 2 are shown the preoperative curves of these and a few other curves of cases in which operation was not performed, all of which have been superimposed and to which reference has been made in the section on "Sugar Tolerance." Chart 3 presents the superimposed postoperative curves of the six cases, and shows the distinct lowering of the blood sugar levels when contrasted with chart 2.

The six patients selected for this study included one with mild clinical diabetes (case 1) whose curve improved strikingly. The others were all typical acromegalic patients without diabetes who had preoperative tests, and who had varying amounts of their chromophile adenomas removed at operation. It is of significance that the patient (case 2) in whom the improvement in the sugar tolerance was most marked had the most radical operation of the entire group; also that the patients whose postoperative increase in tolerance was least marked had the least amount of tissue removed at operation.

In addition to the increase in sugar tolerance, moreover, these patients all showed a distinct improvement in the outward manifestations of

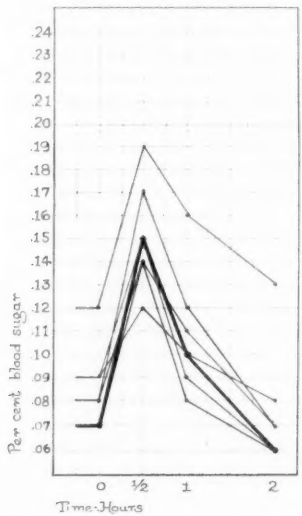

Chart 3.—Postoperative blood sugar tolerance curves in six cases included in chart 2, showing distinct lowering in sugar levels. (Increase in sugar tolerance).

their acromegaly, such for example as a decrease in the size of the hands and feet owing to the disappearance of the peculiar thickening of the soft parts so characteristic of active acromegaly. Still another concomitant change has been the lowering of the basal metabolic rate following operation, which we have been led to interpret as a manifestation of reduction in pituitary activity.[3]

We may therefore deduce from these observations: (1) that the function of metabolizing carbohydrates is frequently impaired in acromegaly, amounting in many cases to actual clinical diabetes mellitus; and (2) that measures taken to reduce the hyperactivity of the pituitary anterior lobe seem to have a beneficial effect on the patients' ability to handle sugars.

Whether these findings indicate that the hypophysis may directly influence the capacity of the body to utilize carbohydrates, or whether the effect occurs only through some secondary disturbance of the glycolytic function of the pancreatic islets, there is as yet no positive way of determining. We are inclined to favor the latter view, but in either case the hypophysis so far as we can see plays the leading rôle.

In H. M. Evans' Harvey Lecture for 1924 on "The Function of the Anterior Hypophysis" he states:

> The hypophysis stands in a necessary relationship to the normal function of the thyroid, sex glands and adrenal cortical tissue. Any explanation of how these effects are mediated constitutes part of the ill-understood field of chemical dependencies and correlation within the body, ignorance of which cannot properly place in doubt evidence that correlation exists.

To these three subsidiary endocrine organs that Dr. Evans mentions, of whose activity the hypophysis is a regulator, we may definitely add the pancreatic islets, and may further state that in hyperpituitarism (acromegaly) the inter-reaction so far as the thyroid (and possibly the parathyroid) and suprarenal cortex are concerned is an acceleration of function. It is possible that this may also be true of the pancreatic islets and of the sex glands as well, even though symptomatically they show respectively the amenorrhea and relative hyperglycemia commonly interpreted as evidences of lowered function. The amenorrhea, however, as Evans has shown, may be otherwise explained; and the hyperglycemia may merely be an indication of temporary exhaustion of the islets from overstimulation and thus represent a condition from which recovery is possible.

SUMMARY AND CONCLUSIONS

It is coming to be the consensus of opinion of those who have concerned themselves with the subject, that acromegaly represents a state of hyperpituitarism which is ascribable to the overaction of the acidophilic cells of the pars anterior. With this opinion our studies as presented in previous numbers of this series are in full agreement.

It has been emphasized in a paper dealing with the findings in four autopsied cases that hyperpituitarism as represented by acromegaly stands apart from other endocrine disorders in its striking secondary effects on the other ductless glands, notably in an adenomatous hyperplasia of the thyroid, in an hypertrophy or adenomatosis of the suprarenal cortex, and in adenomatous changes in the parathyroids.

In addition to these hypertrophic changes, a diminished functional activity affects the gonads and similarly there appears to be diminished power of metabolizing carbohydrates which is generally assumed to be the sole function of the pancreatic islets.

In a discussion of the increased basal metabolic rate seen in the disease the stand was taken that this was primarily a hypophysial disturbance even though the thyroid without doubt was secondarily affected. The substantiation for this view was the definite lowering of the metabolic rate following partial extirpations of hypophysial adenomas.

There are ample reasons to support the belief that the melituria which occur in about 25 per cent of all cases of acromegaly may be similarly accounted for as primarily hypophysial, even though the pancreatic islets doubtless play a secondary rôle in their production. To be sure, the diabetes of acromegaly responds to insulin just as the increased basal metabolic rate of acromegaly responds to Lugol's solution. But neither of these responses appear to be quite so definite as are the responses in primary pancreatic diabetes to insulin and in primary exophthalmic goiter to Lugol's solution.

We may conclude that the glycosurias which accompany acromegaly are ascribable primarily to the hyperpituitarism for the following reasons:

1. Patients with acromegaly (hyperpituitarism) even in the absence of spontaneous glycosuria usually have a low sugar tolerance and tend to show some measure of hyperglycemia, whereas patients with the reverse condition (hypopituitarism) usually have a high tolerance for sugars and ordinarily show definite hypoglycemia.

2. Though the melituria of acromegaly may terminate as ordinary diabetes does in a state of coma, the condition nevertheless shows marked variability in its degree of intensity and appears to be spontaneously recoverable, which is seldom if ever true of primarily pancreatic diabetes.

3. Insulin and posterior lobe extracts have been shown to be, and insulin and active anterior lobe extracts may be presumed to be, counteractive in their effects. Whether in acromegaly the melituria is due to an excess of posterior lobe extract, as the counter-effects on insulin would appear experimentally to indicate, or to an overactivity of the acidophilic cells of the anterior lobe as we are inclined to believe, or possibly to a combination of both, for we know little of the source of the active substance of the posterior lobe, time will surely tell. Hyperpituitarism in any case produces a substance which enters the circulation and counteracts the normal functional activity of the pancreatic islets, glycosuria being the frequent consequence.

4. Insulin will control acromegalic diabetes, but far less effectively than it does the more common forms of diabetes unassociated with hyperpituitarism, the assumption being that the increased pituitary activity tends to counteract its effects.

5. The partial extirpation of the acromegalic adenoma by surgical procedures will apparently render patients with diabetes more amenable to insulin and may promptly lower the tendency to hyperglycemia exhibited by many of these patients even in the absence of active glycosuria. It may be anticipated that more radical procedures than those customarily undertaken, now that the operation has become reasonably safeguarded and perfected, will similarly serve to reduce the hyperpituitarism to such a degree as to check effectually and permanently actual acromegalic glycosuria or possibly even acromegalic diabetes.

THE INFLUENCE OF MENSTRUATION ON THE CONCENTRATION OF CALCIUM IN BLOOD PLASMA *

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Over thirty-five years ago Fehling [1] showed a relationship between ovarian function and calcium metabolism by demonstrating the curative action of oophorectomy on osteomalacia following pregnancy. With the development in recent years of satisfactory microchemical methods for the estimation of the inorganic constituents in blood, calcium has been receiving ceaseless attention with a view to establishing the manner of its manifold operation in the animal economy. Among the many such studies, some have been directed toward investigations of the influence of the menstrual cycle on the concentration of calcium in blood.

We do not propose herein to discuss the literature pertinent to this topic, nor to undertake the recital of the many theories offered by investigators in explanation of their varied observations. The present status of the conclusions in this problem may be accepted as indicated in three recent publications, those by Rittmann,[2] Schultze [3] and Heyn and Haase.[4] From these one infers that while the menstrual cycle does influence the level of the blood calcium, such an influence is not always in the same direction nor operative in all women to the same degree. A distinct weakness is present in all the studies thus far reported in that in the effort to demonstrate the extent and manner of the cyclic influence of menstruation no attempt has been made to secure a series of consecutive specimens of blood from the same subject. Such data are presented in this article.

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1. Fehling, H.: Ueber Wesen und Behandlung der Puerperalen Osteomalakie, Arch. f. Gynäk. **39**:171, 1891.

2. Rittmann, R.: Blutcalzium Spiegel und Menstruation, Wein. Arch. f. inn. Med. **8**:261 (July) 1924.

3. Schultze, G. K. F.: Ovarialtätigkeit, Kalium-Calcium Gehalt des Blutserums und Vegetatives System, Arch. f. Gynäk. **126**:35 (Jan.) 1924-1925.

4. Heyn, A., and Haase, K.: Ueber die Beziehungen der Ovarialfunktion zum kalkgehalt des Blutserums, Arch. f. Gynäk. **126**:646, 924-1925.

METHOD

The subjects studied were three women who menstruated regularly and who, aside from the usual accompanying physiologic unrest, were in no way inconvenienced by it. They were requested to record the dates of the onset and course of each menstruation, as well as the time and character of the symptoms observed. The interval between successive menstruations usually being a multiple of seven days, we endeavored to take specimens of blood every six days, thus hoping to vary continually the time relationship of the specimen of blood to the first day of menstruation. These specimens were taken before breakfast, a minimum amount of citrate being used as an anticoagulant.

Plasma calcium,[5] chlorine on whole blood and corpuscular volume were estimated in each specimen. Chlorine was determined in order to supply values on an ion whose variations were, as far as is known, independent of the influences we were studying, thus affording a further basis for interpretation of the variations in the cation calcium. Records on the corpuscular volume served to disclose the influence of hydremia or its opposite when operative on the concentration of calcium which is confined chiefly to the plasma.

A study of the protocols given by our three subjects indicated that those symptoms in each instance referable to what we have called the physiologic unrest accompanying menstruation anticipated the onset of menstruation by from several days to a week, and maintained themselves in one form or another throughout the menstrual period and even beyond. Although we may appreciate that in introspective analysis of this kind overzealous subjects may tend to overestimate the time factor in the effects recorded, it seems fair to accept for purposes of interpretation of our data a division of the twenty-eight to thirty day cycle into a menstrual half, covering the seven to eight days preceding and succeeding the date of onset of flow, and an intermenstrual half, covering the remaining days of the cycle.

Subject 1 was a laboratory technician, aged 36, German, blond, unmarried, 5 feet and 1 inch in height, weighing 105 pounds (47.6 Kg.).

Subject 2 was a nurse, aged 31, American, brunette, married nine years, and had had one pregnancy. She was 5 feet and 3 inches in

5. Kramer, B., and Tisdall, F. E.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475 (Aug.) 1921. Whitehorn, J. C.: Simplified Method for the Determination of Chlorides in Blood or Plasma, J. Biol. Chem. **45**:449 (Feb.) 1921. (Chlorine was estimated on whole blood; this is compulsory for securing acceptable values when no attempt is made to control the interchange of chlorine between corpuscles and plasma as influenced by the partial carbon dioxide pressure of laboratory environment.)

height, and weighed 175 pounds (79.4 Kg.). She was distinctly obese and plethoric.

Subject 3 was a nurse, aged 33, American, blonde, 5 feet and 10 inches in height, weighing 126 pounds (57.2 Kg.). She was conspicuously long-boned.

In tables 1, 2 and 3 are contained the analytic data on the specimens of blood of these three subjects. A study of these data indicates, first, that the concentrations of calcium are independent of plasma corpuscle ratios; second, that no correlation exists between the variations in measures of chlorine and calcium; and third, that the highest concentrations of calcium seem distinctly to be confined to those days of the twenty-eight to thirty day cycle defined in the foregoing as the menstrual half.

In table 4 the data concerning the chlorine and calcium content of the blood are expressed as percentages of the lowest figure in each series; this at once demonstrates that the variations in chlorine and calcium are independent and of a different order.

In table 5 the data concerning the chlorine and calcium content of the blood of each subject are segregated in two groups, those belonging to the menstrual and those belonging to the intermenstrual periods as defined in the foregoing. It further emphasizes the variations of chlorine concentration as independent of the menstrual cycle and shows the consistent tendency of the blood calcium to maintain itself at a higher concentration during the menstrual half of the month.

COMMENT ON AND DETAILED ANALYSIS OF DATA

Duplicate estimates of calcium on specimens of blood gave values that differed by less than 0.15 mg. per hundred cubic centimeters. Five times this amount (0.75 mg. per hundred cubic centimeters) may safely be accepted as indicative of a significant change in concentration.

Subject 1.—The first recorded menstrual days, April 30 to May 2 inclusive (three days), reflected no influence on the concentration of calcium. Unfortunately, however, the two specimens of blood taken nearest these dates covered the third day before the onset and one day after the completion of flow, and, under the circumstances, a significant influence on the concentration of calcium might have occurred during the six day interval between the days when these two specimens of blood were taken. On May 26, two days before the next menstrual flow, the blood increased 1.25 mg. over that of the preceding specimen, reaching 10.79 mg., and maintained this level through June 1, the last of a five day flow. On June 22, the first day of flow of the third menstrual period, the blood again showed a significantly high calcium content (10.22 mg.), a rise of 1.29 mg. over the preceding specimen.

TABLE 1.—*Corpuscular Volume, Whole Blood Chlorine and Plasma Calcium as Estimated in Subject 1*

Date	Corpuscular, per Cent by Volume	Whole Blood Chlorine as Sodium Chloride, Mg. per 100 Cc.	Plasma Calcium, Mg. per 100 Cc.
4/15/26	....	...	9.92
4/21/26	....	...	9.44
4/27/26	40.0	532	9.22
4/30/26 (first day of menstruation)			
5/ 2/26 (last day of menstruation)			
5/ 3/26	39.3	554	9.26
5/ 8/26	38.0	490	9.22
5/14/26	39.4	490	9.36
5/20/26	39.1	499	9.54
5/26/26	38.5	474	10.79
5/28/26 (first day of menstruation)	40.8	499	10.89
6/ 1/26 (last day of menstruation)	45.0	495	10.94
6/ 7/26	40.1	482	9.52
6/12/26	36.4	490	8.71
6/18/26	40.0	507	8.93
6/22/26 (first day of menstruation)	38.4	...	10.22
6/24/26	45.1	515	9.95
6/26/26 (last day of menstruation)			
6/30/26	40.6	482	9.44

TABLE 2.—*Corpuscular Volume, Whole Blood Chlorine and Plasma Calcium as Estimated in Subject 2*

Date	Corpuscular, per Cent by Volume	Whole Blood Chlorine as Sodium Chloride, Mg. per 100 Cc.	Plasma Calcium, Mg. per 100 Cc.
4/12/26	....	...	8.99
4/19/26	....	...	8.90
4/24/26	....	...	8.99
4/30/26	46.1	...	9.06
5/ 1/26 (first day of menstruation)			
5/ 5/26 (last day of menstruation)			
5/ 7/26	....	482	9.49
5/13/26	41.7	482	9.36
5/20/26	41.8	485	9.27
5/26/26	40.5	482	9.17
6/ 2/26 (first day of menstruation)	42.6	465	10.60
6/ 5/26 (last day of menstruation)			
6/ 8/26	43.6	482	9.04
6/15/26	48.1	492	8.98
6/21/26 (appearance of menstrual symptom, enlargement of breasts)			
6/23/26	41.7	...	10.13
6/30/26	48.3	474	8.91
7/ 1/26 (first day of menstruation)			

TABLE 3.—*Corpuscular Volume, Whole Blood Chlorine and Plasma Calcium as Estimated in Subject 3*

Date	Corpuscular, per Cent by Volume	Whole Blood Chlorine as Sodium Chloride, Mg. per 100 Cc.	Plasma Calcium, Mg. per 100 Cc.
4/20/26 (first day of menstruation)	....	...	9.67
4/26/26 (last day of menstruation)	47.8	561	9.56
5/ 1/26	40.0	569	9.06
5/ 7/26	38.0	...	9.33
5/13/26	39.5	507	11.32
5/15/26 (first day of menstruation)			
5/19/26	35.5	565	9.60
5/21/26 (last day of menstruation)			
5/25/26	35.2	532	9.36
6/ 1/26	45.0	515	9.55
6/ 7/26	41.7	532	9.39
6/11/26 (first day of menstruation)			
6/12/26	39.6	540	9.15
6/18/26 (last day of menstruation)	40.6	533	8.88
6/24/26	39.0	490	9.04
6/30/26	41.7	524	9.07

TABLE 4.—*Chloride and Calcium Expressed as a Percentage of the Lowest Measure in the Series for Each Subject Respectively*

Subject 1		Subject 2		Subject 3	
Calcium	Chloride	Calcium	Chloride	Calcium	Chloride
114	...	101	...	109	...
108	...	100	...	108	114
106	112	101	...	102	116
106	117	102	...	105	...
106	105	107	104	128	104
107	103	105	104	108	115
110	105	103	105	105	109
124	100	104	104	108	105
125	105	119	100	106	109
126	104	102	104	103	110
110	102	101	106	100	109
100	103	113	...	102	100
114	107	100	102	102	107
118	...				
114	109				
108	102				

TABLE 5.—*Values for Chloride and Calcium (Mg. per One Hundred Cubic Centimeters Blood) Arranged According to Menstrual and Intermenstrual Grouping (See Text)*

	Menstrual		Intermenstrual	
	Calcium	Chloride	Calcium	Chloride
Subject 1.....	9.22	532	9.92	...
	9.26	534	9.44	...
	10.79	474	9.22	490
	10.80	499	9.36	490
	10.94	495	9.54	499
	8.93	507	9.52	482
	10.22	...	8.71	490
	9.95	515		
	9.44	482		
Average.....	9.96	507	9.39	492
Subject 2.....	9.66	...	8.99	...
	9.49	482	8.90	...
	9.17	482	8.99	...
	10.60	465	9.36	482
	9.04	482	9.27	485
	10.13	...	8.98	492
	8.91	474		
Average.....	9.49	477	9.08	486
Subject 3.....	9.67	...	9.06	569
	9.56	561	9.33	...
	11.32	507	9.36	532
	9.60	565	9.55	515
	9.39	532	9.04	490
	9.15	540		
	8.88	533	9.07	524
Average.....	9.65	540	9.24	526
Average all subjects..	9.72	509	9.23	504

Forty-eight hours later, and still during the menstrual flow, this high level was maintained. The records in this case are suggestive of the inference that the concentration of calcium in the blood rises shortly before the menstrual flow and drops again after it.

SUBJECT 2.—In this subject's records only two significant rises in the concentration of calcium appeared. On June 2, the first day of menstrual flow, a rise of 1.43 mg. over that of the preceding record occurred, disappearing in the next specimen taken two days after a five day flow. The second significant rise, June 23, 1.15 mg. over the concentration of the preceding sample, occurred eight days before the onset of the menstrual flow but forty-eight hours after the appearance of a menstrual symptom (engorgement of the breasts). The last record of this series, taken twenty-four hours before the first day of flow, showed a drop to the normal level. The relationship of high blood calcium to the menstrual period is not convincingly brought out in this case; still, the two recorded rises not only are within the fourteen days ascribed to the menstrual half of the cycle, but are also definitely related in the one case to the onset of flow, and in the other to the appearance of the physiologic unrest accompanying menstruation.

SUBJECT 3.—In this subject there is one record on the first day of flow and another forty-eight hours before the onset of flow. These are the two highest concentrations in the series; 9.67 mg. (April 20) and 11.32 mg. (May 13). Of these two, only the latter can be accepted as appreciably high. No menstrual influence is discernible in the concentration of calcium for the last recorded menstrual cycle, June 11 to June 18; but, if in this subject we were dealing with a premenstrual elevation of calcium that quickly dissipated itself within the first day or so of flow, all trace of a menstrual influence might be lost in the specimens of June 7 and 12.

In 1908, Blair Bell,[6] determining the calcium content by the crude procedure of counting, in a hemocytometer, the crystals of calcium oxalate precipated on the addition of oxalate to the blood, reported a sudden rise in blood calcium just before menstruation and presented the hypothesis that this change in the blood picture touched off, so to speak, the rhythmic function of uterine bleeding. He carried the matter further by ascribing to the uterus the function of a calcium-secreting organ, thereby indicating it as the mammalian analogue to the avian calcium-secreting gland. Riddle[7] has recently demonstrated the tremendous increases in calcium in the blood of birds in anticipation of ovulation.

6. Bell, Blair: Menstruation and Its Relationship to the Calcium Metabolism, Proc. Roy. Soc. Med. **1**:291, 1907-1908.

7. Riddle, O., and Reinhart, Warren, H.: Studies on the Physiology of Reproduction in Birds. Blood Calcium Changes in the Reproductive Cycle, Am. J. Physiol. **76**:660 (May) 1926.

In attempting an interpretation of such data as we here present, at least two glands of internal secretion must be taken into consideration, the ovary and parathyroid—the one with unquestioned influence on menstruation and the other of equally certain influence on the concentration of calcium in the blood. We refer the reader to Corner's [8] excellent review for a summary of the physiologic researches covering pertinent features of ovarian function (ovulation, oestrus and menstruation). Our knowledge of parathyroid activity in conjunction with that of the gonads is yet too meager to merit discussion.

CONCLUSION

Although our data have failed to produce with convincing rhythmicity a rise in the concentration of calcium in the blood at the approach and onset of menstruation, they present strong evidence that such a rise probably occurs. This evidence is as strong, possibly, as one could hope for in the presence of the many other concomitant uncontrolled arrhythmic influences operative on blood calcium.

8. Corner, George W.: Oestrus, Ovulation and Menstruation, Physiol. Rev. **3**:457 (Oct.) 1923.

THE PROTEIN TEST FOR UREA FORMATION FUNCTION OF THE LIVER

PRELIMINARY REPORT *

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The multiple diverse functions of the liver have given rise to correspondingly numerous and diverse tests for these functions. These tests have been reviewed recently by several authors [1] and evaluated in cases of clinical disease and in experimentally produced hypofunction of the liver. In spite of the fact that one of the most important functions of the liver is the deaminization of amino-acids and their conversion to urea—a phase of the physiology of the liver which during the past few years has received much attention and investigation—a standard test for the conversion of urea by the liver has not been elaborated. The hepatic metabolism of carbohydrates,[2] dye elimination,[3] pigment metabolism,[4] detoxifying powers,[5] excretion of urobilin [6] and its other func-

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1. Bauman, Louis: The Physiological and Pathological Chemistry of the Liver; Endocrinology and Metabolism, New York, D. Appleton & Co., 1922, vol. 4, p. 643. Greene, C. H.; Snell, A. M., and Walters, Waltman: Diseases of the Liver: I. Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925; Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, ibid. **36**:274 (Aug.) 1925. Mann, Frank C., and Bollman, Jesse L.: Liver Function Tests, Arch. Path. **1**:681 (May) 1926.

2. Bauman, Louis (footnote 1). Green, C. H.; Snell, A. M., and Walters, Waltman (footnote 1). McLean, H., and de Wesselow, C. L. V.: The Estimation of Sugar Tolerance, Quart. J. Med. **14**:103, 1920.

3. Rosenthal, S. M.: An Improved Method for Using Pheloltetrachlorphthalein as Liver Function Test, J. Pharmacol. & Exper. Therap. **19**:385, 1922. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 11) 1925. Kerr, W. J.; Delprat, G. D.; Epstein, N. N., and Dunievits, Max: The Rose Bengal Test for Liver Function; Studies on the Rate of Elimination from the Circulation in Man, J. A. M. A. **85**:942 (Sept. 26) 1925.

4. Van den Bergh, A. A. H.: La recherche de la bilirubine dans le plasma sanguin par la methode de la reaction diazoique, Presse méd. **29**:441, 1921. McNee, J. W.: Jaundice, Review of the Recent Work, Quart. J. Med. **16**:390, 420 (July) 1923. Andrews, C. H.: The van den Bergh Test in Jaundice, Quart. J. Med. **18**:69, 19 (Oct.) 1924. Bernheim, A. R.: The Icterus Index (The Quantitative Estimation of Bilirubinemia), Its Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1922.

5. Pelkan, K. F., and Whipple, G. H.: Studies of Liver Function: III. Phenol Conjugation as Influenced by Liver Injury and Insufficiency, J. Biol. Chem. **1**:513, 1922. Delprat, G. D., and Whipple, G. H.: Studies of Liver Function, Benzoate Administration and Hippuric Acid Synthesis, J. Biol. Chem. **49**:229, 1921.

tions, including its rôle in ammonia formation,[7] have been the physiologic bases of corresponding tests,[1] but the function of urea formation has largely been neglected.

From 1911 to 1917, Van Slyke,[8] with various collaborators, studied the relation of the liver to the metabolism of proteins. He determined the curve of blood urea after a good sized meal of meat.[9] It was also found that the blood urea rose almost at the minute the first particle of food entered the duodenum, as shown by roentgenograms.[9] This point has been corroborated recently by Morgulis[10] through simultaneous determinations of the blood amino-acids and the blood urea after a protein meal, the urea increasing before the amino-acid content of the blood did, or, in other words, before the food was absorbed from the intestine. Mann and his co-workers[11] of the Mayo Clinic have shown, by extirpation of the liver, that urea formation ceases in the absence of the liver. The urea of the blood and tissues decrease rapidly so that only minimum amounts of urea are present twelve hours after total removal of the liver. Coincident with the cessation of urea formation, amino-acids accumulate in the blood and tissues, but not in proportion to the decrease of urea. The fact that muscles readily absorb amino-acids may explain this discrepancy. Through the medium of an Eck's fistula, Mann and his associates then tested the urea formation function of dogs deprived of most of their hepatic tissue or suffering from injury of the liver. Milk and meat were fed in abundance. Their method was to determine the

6. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. The Quantitative Determination of Urobilin, J. Exper. Med. **41**:503 (April) 1925: II. Derivation of Urobilin, ibid. **41**:513, 719 (June) 1925: ibid. **42**:99 (July) 1925; ibid. **42**:619 (Nov.) 1925. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilin in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925. McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology: VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, J. Exper. Med. **43**:753 (June) 1926.

7. Burchi, R.: Blood Ammonia as a Gage of Liver Function: Folia Clin. Chim. et Micro., Milan: 1-3, 1926; abstr., J. A. M. A. **87**:8 (Aug. 21) 1926.

8. Van Slyke, D. D., and Meyer, G. M.: The Amino Acid Nitrogen of the Blood; Preliminary Experiments on Protein Assimilation, J. Biol. Chem. **12**: 399, 1912-1913; The Fate of Protein Digestive Products in the Body: III. The Absorption of Amino-Acids from the Blood by the Tissues, J. Biol. Chem. **16**: 197, 1913-1914; The Fate of Protein Digestion Products in the Body: The Locus of Chemical Transformation of Absorbed Amino-Acids, J. Biol. Chem. **16**:213, 1913; The Locus of Chemical Transformation of Absorbed Amino-Acids, J. Biol. Chem. **16**:213, 1913-1914. Van Slyke, D. D.; McLean, F. C., and Cullen, G. E.: The Formation of Urea in the Liver, Proc. Soc. Exper. Biol. & Med. **12**:93, 1915. Van Slyke, D. D.: The Chemistry of the Proteins and Their Relation to Disease, Oxford Med. **1**:258, 1920.

9. Van Slyke, D. D.; McLean, F. C., and Cullen, G. E. (footnote 8).

10. Morgulis, S.: Blood Changes During Digestion, with Special Reference to Urea Formation, J. Biol. Chem. **66**:353 (Dec.) 1925.

11. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: VIII. Effect of Total Removal of the Liver on the Formation of Urea, Am. J. Physiol. **69**:371, 1924.

urea excreted in the urine in twenty-four hours, and definite though slight diminution of the excretion of urea was found. Leucine and tyrosine were absent from the urine in animals from which the livers had been removed completely, showing that the presence of these amino-acids in acute yellow atrophy is probably caused by necrosis of the liver and not by the excretion of an excess in the blood.

From clinicochemical studies it has long been known that in disease of the liver abnormalities in the intermediary metabolism of proteins occur,[12] analogous for the most part, to changes described by Mann and his associates in their studies in total hepatectomy. In acute yellow atrophy and phosphorus poisoning [13] there is an increase in the amino-acids of the blood and a decrease in the blood urea, while the urine is low in urea content and high in ammonia and amino nitrogen. The liver has evidently lost part of its ability to deaminize and to convert amino-acids to urea. The administration of amino-acids to patients suffering from marked disease of the liver is followed by an increased excretion of amino nitrogen in the urine.[14] Urea is decreased in the urine of patients with eclampsia [15] when the predominant pathologic change is a degeneration of the liver. Since all tissues, especially muscles,[16] absorb amino-acids, it is not surprising that mild or moderate instances of disease of the liver do not reveal an increase of amino-acids in the blood.

Most of the present tests for liver function are not without equivocation. For instance, changes in glucose, galactose, or levulose tests may be caused by pancreatic disease as well as by disease of the liver.[17] Increase of the bilirubin of the blood or urobilin of the urine may be caused by increased blood destruction as well as by disease of the liver.[18]

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12. Tileston, W., and Comfort, C. W.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Method, Arch. Int. Med. **14**:620 (Nov.) 1924. Chesney, A. M.; and Marshall, E. K., and Rowntree, L. G.: Studies in Liver Function, J. A. M. A. **63**:1533 (Oct. 31) 1914.

13. Bauman, Louis (footnote 1). Van Slyke and Others (footnote 8). Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver. Endocrinology and Metabolism, Arch. Int. Med. **25**:693 (June) 1920.

14. Bauman, Louis (footnote 1).

15. Bauman, Louis (footnote 1). Van Slyke, D. D., and Losee, J. R.: The Toxemia of Pregnancy, Am. J. M. Sc. **153**:94, 1917.

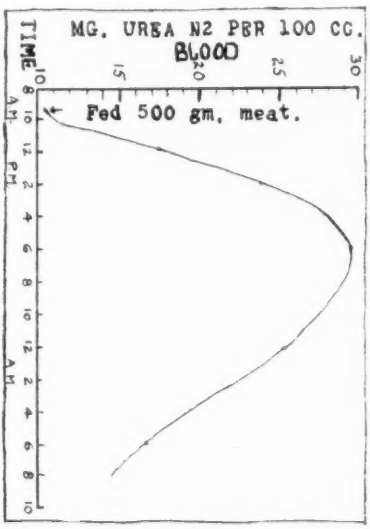
16. Van Slyke, D. D., and Meyer, G. M.: The Fate of Protein Digestive Products in the Body: III. The Absorption of Amino-Acids from the Blood by the Tissues, J. Biol. Chem. **16**:197, 1913-1914.

17. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 289.

18. Van den Bergh, McNee and Andrews (footnote 4). Elman, R., and McMaster, P. H.: Studies on Urobilin Physiology and Pathology: I. The Quantitative Determination of Urobilin, J. Exper. Med. **41**:503 (April) 1925; II. Derivation of Urobilin, ibid. **41**:513, 719 (June) 1925; ibid. **42**:99 (July) 1925; ibid. **42**:619 (Nov.) 1925.

Dyes may be eliminated or absorbed by organs and tissues other than the liver,[19] but the recent work of Mann and his co-workers has shown that the liver is the only organ that has noticeable ability to deaminize and to form urea.[11] Hence there is a potential test that is beyond dispute.

In disease of the liver the determination of the amino-acids, the ammonia of the blood or the urinary amino nitrogen is a complex task; it is not a perfect test for the reason previously given, namely, that tissues absorb amino-acids. The estimation of the urea excreted in twenty-four hours after a heavy meal of meat or milk is not a delicate criterion, for time is allowed for readjustments and compensations, and thus a lag in excretion may readily be overlooked.



Time curve of changes in the blood urea during protein digestion. (After Van Slyke, Oxford Med. **1**:264, 1920).

As stated before, Van Slyke[20] found a typical curve of blood urea after a protein meal which is reproduced in the chart. It will be noted that in four hours the blood urea is about doubled, and in eight hours it is about trebled, after a meal of approximately 1.5 Gm. of protein per kilogram. Apparently this was a proper basis for protein tests for liver function. Since we were dealing with children, and sick or convalescent children as a rule, we did not think it expedient to take frequent specimens of blood. Accordingly, we experimented until we

19. Rosenthal, S. M., and White, E. C. (footnote 3).
20. Van Slyke, D. D.; McLean, F. C., and Cullen, S. E. (footnote 8). Van Slyke, D. D. (footnote 8).

found that four hours after the protein meal was the most satisfactory time to take the second specimen of blood in children. At this time we could detect the earliest appreciable rise, thereby discovering any lag akin to the glucose tolerance test. Six and eight hour intervals only showed further rise or a continued low blood urea and compensatory rises. We also found it impracticable to feed a child more than 1 Gm. of protein per kilogram, which is usually preferred in the form of chicken, the white part being the portion of choice because of its low fat content, but the dark meat may be given if the child prefers it.

AUTHOR'S METHOD OF PERFORMING TESTS FOR LIVER FUNCTION

For the purposes of this study, cases of obvious liver injury were selected, but we also investigated cases in which there was reason to suspect disturbed function of the liver. To check our results, other proved and accepted tests for liver function were employed at the same time. The figures of accepted results of these tests were used as standard.[21] A series of control cases with apparently normal function of the liver was studied. After trying various methods, our final procedure was as follows:

1. While the patient was fasting a specimen of blood was taken for: (*a*) blood sugar, (*b*) blood urea, (*c*) quantitative determination for bilirubin (the van den Bergh test), and (*d*) use as standard for dye test.

2. Dye was then injected intravenously. At first the phenoltetrachlorphthalein dye was used, but later we used bromsulphalein because venous thrombosis was frequently caused by the first dye, and because of possible deleterious results like those reported in the literature.[22]

3. Blood was withdrawn for determination of the dye in fifteen minutes and in one hour for the phenoltetrachlorphthalein test or in thirty minutes for the bromsulphalein test.

4. Levulose was given, 1.5 Gm. per kilogram. The blood sugar was then determined every half hour for two or three hours.

5. The protein meal was given, 1 Gm. per kilogram, and the blood urea taken four hours later.

6. Twenty-four hour urinalyses were made to determine the amount of urobilin. At first we used the Wallace-Diamond test,[23] but later we employed the more satisfactory Joyce test as modified by Kuttner.

In this way all our tests could be performed in one day, and thus easily repeated when changes in the clinical condition occurred. Checks showed that the tests so performed did not interfere with the results.

As a control series we used children who were suffering from a disease that we were clinically certain did not affect the function of the liver. The effect of a protein meal on the blood urea was studied at two and four hour intervals after the ingestion of the meal, and occasionally six hour studies were made. The results of these tests are shown in table 1.

From the figures in table 1 it will be observed that a two hour interval between the protein meal and the determinations for blood

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21. McLean, H., and de Wesselow, C. L. V. (footnote 2). Rosenthal, S. M. (footnote 3). Rosenthal, S. M., and White, E. C. (footnote 3). Van den Bergh, A. A. H. (footnote 4). Wallace, G. B., and Diamond, J. S. (footnote 6).

22. Rosenthal, S. M., and White, E. C. (footnote 3). Rosemau, W. H.: Dangers in the Use of Certain Halogenated Pthaleins as Functional Tests, J. A. M. A. **85**:2017 (Dec 26) 1925.

23. Wallace, G. B., and Diamond, J. S. (footnote 6).

urea produced an inconstant rise which was not nearly so satisfactory as a four hour interval when the increase of the blood urea above the fasting level was marked and fairly constant. The percentage of increase varied from 62 per cent to 133 per cent, with an average of 90 per cent. The general trend of the increase was around two levels, 70 per cent to 75 per cent and 100 per cent to 120 per cent. To be on the safe side, at this stage we have made our standard of normalcy in this test for liver function in children an increase of at least from 50 to 60 per cent above the fasting blood urea four hours after a protein meal of 1 Gm. per kilogram. The work of Van Slyke[9] and his

TABLE 1.—*Increase in Blood Urea After Protein Meal in Children with Apparently Normal Livers*

No.	Name	Sex	Weight, Kg.	Diagnosis	Protein Eaten, Gm.	Blood Urea Nitrogen per 100 Cc. Blood	Increase of Blood Urea in 4 Hours, per Cent
1	R. M.	M	22	Malnutrition	22	Fasting, 11.2 mg. 2 hours, 12.0 mg. 4 hours, 19.6 mg.	75
2	H. G.	M	38	Chorea	38	Fasting 12.0 mg. 2 hours, 14.0 mg. 4 hours, 21.0 mg.	75
3	M. B.	M	40	Herpes	40	Fasting, 12.6 mg. 2 hours, 14.0 mg. 4 hours, 21.0 mg.	70
4	A. W.	M	21	Chorea	21	Fasting, 11.2 mg. 4 hours, 18.2 mg.	62
5	H. H.	M	32	Postencephalitis	32	Fasting, 11.2 mg. 2 hours, 19.6 mg. 4 hours, 23.8 mg.	112
6	L. R.	M	23.5	Chorea	23.5	Fasting, 11.0 mg. 2 hours, 12.4 mg. 4 hours, 19.4 mg.	76
7	E. D.	F	26	Hernia	26	Fasting, 12.6 mg. 2 hours, 26.4 mg. 4 hours, 29.4 mg.	133
8	C. C.	F	31	Mild convalescent rheumatism	31	Fasting, 15.4 mg. 2 hours, 21.0 mg. 4 hours, 33.6 mg.	121
9	R. L.	F	27.5	Mild rheumatism	27.5	Fasting, 14.0 mg. 4 hours, 25.0 mg.	79

co-workers and of Morgulis,[10] which showed an immediate deaminization and urea formation by the liver after a protein meal, led us to conduct a short investigation to determine whether this was a specific effect of the protein or whether it was the stimulus of any food on this function of the liver. Accordingly, in three of our control cases we determined the blood urea at two and four hour intervals after a glucose meal. The results are given in table 2.

From the foregoing figures we see that the ingestion of glucose did not affect the blood urea, and we must conclude that the protein or amino-acid molecule alone in the intestinal tract has the faculty of stimulating the liver to deaminization before the amino-acid of the blood is increased.

In table 3 are summarized the results of tests for liver function in cases in which there was definite hepatic disorder both during and after the liver was injured. The first was a case of pneumonia which was marked by jaundice and large liver. All tests for liver function yielded subnormal results, while the liver was enlarged and the patient icteric.

TABLE 2.—*Increase in Blood Urea after Glucose Meal in Children with Apparently Normal Livers*

No.	Name	Sex	Weight, Kg.	Diagnosis	Glucose Ingested, Gm.	Blood Urea Nitrogen per 100 Cc. Blood	Increase of Blood Urea in 4 Hours, per Cent
1	L. R.	M	23.5	Chorea.....	53	Fasting, 12.4 mg. 2 hours, 11.2 mg. 4 hours, 12.6 mg.	0
2	F. D.	F	26	Hernia.....	60	Fasting, 14.0 mg. 2 hours, 14.0 mg. 4 hours, 14.0 mg.	0
3	C. C.	F	31	Rheumatism.....	70	Fasting, 11.0 mg. 2 hours, 12.4 mg. 4 hours, 11.9 mg.	0

TABLE 3.—*Tests for Liver Function in Children with a Definite Pathologic Condition of the Liver as Evidenced by Jaundice and Large Liver*

Name	Sex	Weight, Kg.	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test	Van den Bergh Test	Urine Urobilin
R. J.	M	36	12/14/25	Fasting, 18.2 mg. 4 hours, 18.2 mg. Increase, 0	.....	15 min. 25% 1 hour 20% (P. T. P.)	1:40,000	Present 1:800 dilution
			12/23/25	Fasting, 11.2 mg. 4 hours, 16.8 mg. Increase, 50%	.....	1 hour, 0	1:200,000	Present 1:10 dilution
E. S.	M	30	3/ 1/26	Fasting, 12.6 mg. 4 hours, 15.24 mg. Increase, 22%	0.105 0.100 0.105 0.105	½ hour, 30% 1 hour, 30% (B. S. P.)	1:34,000	Present 1:150 dilution
			3/14/26	Fasting, 14.0 mg. 4 hours, 16.8 mg. Increase, 20%	0.088 0.100 0.110 0.100	½ hour, 10% (B. S. P.)	1:100,000	Present 1:70 dilution
			3/19/26	Fasting, 12.8 mg. 4 hours, 19.4 mg. Increase, 55%	.....	.....	1:300,000	Present 1:10 dilution
W. F.	M	28	8/27/26	Fasting, 14.0 mg. 4 hours, 16.8 mg. Increase, 20%	.....	.....	1:100,000	
			9/ 3/26	Fasting, 14.8 mg. 4 hours, 23.8 mg. Increase, 60%	.....	.....	1:400,000	

Especially to be noted is the fact that at this stage a protein meal did not cause an increase in the blood urea at the end of four hours. After the pneumonia had completely resolved, the jaundice had disappeared and the liver had become normal in size; tests for liver function were normal, including the protein test, which then caused a 50 per cent increase in four hours. The second case is one of so-called catarrhal

jaundice which is now generally regarded as a hepatitis.[24] Tests for liver function during the stage of jaundice and enlarged liver revealed subnormal hepatic function, with the exception of the levulose tolerance test. The protein test caused a 22 per cent increase in the fasting blood urea, which two weeks after remained the same, but which later rose to 55 per cent, or a normal increase, contemporaneously with a return of the blood billirubin to normal. The clinical data at this period of normalcy revealed a liver normal in size and free from icterus. The third patient was suffering from the same disease, and substantially the same results were obtained with these tests.

TABLE 4.—*Children with Cardiac Disease and Enlarged, Tender Liver and Decompensation Showing Changing Tests for Liver Function During and after Decompensation*

Name	Sex	Weight, Kg.	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test (Bromsulphalein)	Van den Bergh Test	Urine Urobilin
E. L.	M	28	3/ 8/26	Fasting, 12.6 mg. 4 hours, 14.0 mg. Increase, 11%	0.100 0.110 0.110 0.100	½ hour, 5%	1:200,000	Absent
			3/19/26	Fasting, 12.6 mg. 4 hours, 19.6 mg. Increase, 55%	.....	.....	1:400,000	
L. B.	F*	23	6/ 8/26	Fasting, 18.2 mg. 4 hours, 22.4 mg. Increase, 22%	.....	.....	1:150,000	
A. W.	M	18	6/14/26	Fasting, 16.8 mg. 4 hours, 18.2 mg. Increase, 8%	0.092 0.135 0.095 0.092	½ hour, neg.	1:300,000	Trace
			6/29/26	Fasting, 12.6 mg. 4 hours, 19.6 mg. Increase, 5%				
A. S.	M	24	5/16/26	Fasting, 11.2 mg. 4 hours, 15.4 mg. Increase, 30%	0.100 0.115 0.110 0.100	½ hour, neg.	1:300,000	Absent
			6/ 3/26	Fasting, 12.6 mg. 4 hours, 18.2 mg. Increase, 45%				
I. S.	M	28	3/19/26	Fasting, 16.8 mg. 4 hours, 18.0 mg. Increase, 7%	.....	½ hour, neg.	1:400,000	Trace
			3/26/26	Fasting, 15.4 mg. 4 hours, 28.0 mg. Increase, 85%				

* Severe cardiac with tremendous liver. The patient died within a short time.

Another group, composed of children with heart disease, was also studied to determine whether the clinical symptoms of an enlarged liver denoting decompensation and the commonly encountered subicteric tint were associated with signs of a lowered function of the liver, as suggested by some workers.[25] For this purpose cases with signs of decom-

24. McNee (footnote 4, second reference) and Andrews (footnote 4, third reference).

25. Andrews, C. H. (footnote 4). Ottenberg, R.; Rosenfeld, S., and Goldsmith, L.: The Clinical Value of the Serum-Tetrachlorphenolphthalein Test for Liver Function, Arch. Int. Med. **34**:206 (Aug.) 1924.

pensation and an enlarged liver were investigated at the same time as cardiac cases without signs of decompensation but with a normal liver according to physical examination. The data are given in table 4.

Analysis of the data reveals that the levulose tolerance tests have been of little value in revealing liver hypofunction. The van den Bergh and the protein tests for urea formation have given positive results. The other liver tests in this group have not thrown much light on the function of the liver. The slight increase in blood bilirubin as shown by the van den Bergh reaction in patients with compensated heart disease is probably due to hemolysis with consequent increase of the blood bilirubin. This is evident by the increasing anemia in rheumatic fever and also suggested by the indirect reaction of the van den Bergh test, as was pointed out by Fishberg.[26] It must be stated here, however, that the latter test is far from an unfailing guide to hemolysis, as shown in

TABLE 5.—*Tests for Liver Function in Cardiac Children not Decompensated, with Impalpable Livers*

Name	Sex	Weight, Kg.	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test	Van den Bergh Test	Urine Urobilin
J. B.	M	22	Fasting, 11.2 mg. 4 hours, 18.2 mg. Increase, 62%	0.160 0.110 0.105 0.100	½ hour, neg.	1:170,000	Absent
R. L.	F	23.5	Fasting, 14 mg. 4 hours, 25 mg. Increase, 78%	0.090 0.105 0.105 0.100	½ hour, neg.	1:200,000	Absent
C. O.	F	31	Fasting, 15.4 mg. 4 hours, 21.0 mg. Increase, 38%	.....	½ hour, neg.	1:300,000	Absent

the cases of decompensated heart disease when other tests indicated that the increased bilirubin was due to diminished hepatic function. A high urea index for the blood in cases of cardiac decompensation when the patient is fasting is known to be due to renal deficiency.

The function of the liver is often disturbed in cases of severe pneumonia. As evidence, we can adduce the clinical facts of hepatic enlargement and jaundice, and the laboratory aid of tests of function in such cases,[27] particularly the retention of dye in toxic cases of pneumonia. With this point in mind, we studied some cases of toxic pneumonia in contrast to mild cases of pneumonia when there was little reason to suspect involvement of the liver, studying the function of the liver immediately after the crisis and again after complete convalescence, when indicated.

26. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, J. A. M. A. **80:** 1516 (May 26) 1923.

27. Ottenberg, R.; Rosenfeld, S., and Goldsmith, L. (footnote 25). Harris, B. R.: Alterations in Liver Function as an Index of Toxemia in Pneumococcus Lobar Pneumonia, J. Clin. Investigation **20:**6 (Aug. 20) 1926.

In cases of toxic pneumonia, the protein test for liver function in three of four cases revealed subnormal urea formation by the liver. In two of these, the van den Bergh test and the increased excretion of urobilin in the urine were further evidence of the impaired function of the liver. Before the children were discharged from the hospital, the protein tests, together with the other tests, had become normal, demonstrating the rapid recovery of the liver in convalescence after pneumonia. The dye test was positive in only one case, and the levulose metabolism was normal in every case. Mild cases of pneumonia revealed little change in the function of the liver. In passing, we may note that the initially high fasting urea sometimes encountered in infections had been noted and commented on previously.[28]

TABLE 6.—*Liver Function Tests in Cases of Toxic Pneumonia*

Name	Sex	Weight, Kg.	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test	Van den Bergh Test	Urine Urobilin
I. L.	M	20	2/ 2/26	Fasting, 14.0 mg. 4 hours, 16.8 mg. Increase, 20%	0.075 0.190 0.100 0.094	½ hour, 0	1:400,000	Absent
			2/15/26	Fasting, 11.0 mg. 4 hours, 18.0 mg. Increase, 65%				
F. S.	F	19	2/26/26	Fasting, 19.6 mg. 4 hours, 33.6 mg. Increase, 74%	0.080 0.100 0.100 0.090	½ hour, 0	1:400,000	Trace
A. S.	F	23.5	3/27/26	Fasting, 14.3 mg. 4 hours, 18.6 mg. Increase, 31%	0.100 0.114 0.115 0.102	½ hour, 0	1:125,000	Absent
			4/10/26	Fasting, 12.4 mg. 4 hours, 21.6 mg. Increase, 77%	.....	.....	1:140,000	
R. J.	M	26	12/14/25	Fasting, 18.2 mg. 4 hours, 18.2 mg. Increase, 0	.....	15 min., 25% 1 hour, 20% (P. T. P.)	1:40,000	1:800 dilution
			12/23/25	Fasting, 11.2 mg. 4 hours, 16.8 mg. Increase, 50%	.....	1 hour, 0	1:200,000	1:10 dilution

TABLE 7.—*Liver Function Tests in Cases of Mild Pneumonia*

Name	Sex	Weight, Kg.	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test	Dye Test (Bromsulphalein)	Van den Bergh Test	Urine Urobilin
C. C.	F	19	12/13/25	Fasting, 11.2 mg. 4 hours, 16.8 mg. Increase, 50%	.....	0	1:400,000	1:10 dilution
E. D.	F	17	1/ 9/26	Fasting, 11.2 mg. 4 hours, 18.0 mg. Increase, 60%	0.110 0.120 0.107 0.105	0	1:200,000	1:10 dilution
H. N.	F	20	2/14/26	Fasting, 18.0 mg. 4 hours, 26.6 mg. Increase, 48%	0.120 0.135 0.105 0.096	½ hour, 5%	1:400,000	Absent

28. Tileston, W., and Comfort, C. W. (footnote 12).

Another group studied was a miscellaneous one in which, however, there was reason to suspect disturbance of the function of the liver. The results are given in table 8.

These results show that a patient who had leukemia and a large liver did not reveal a demonstrable lowering of the function of the liver according to our tests for liver function. A patient with Hodgkin's disease showed a definite diminution of the function of the liver, as shown by increased blood bilirubin, excessive urobilin in the urine and the protein test which resulted in only 27 per cent increase of the blood urea in four hours. A patient suspected of having abdominal tuberculosis with an easily palpable liver showed only a 28 per cent increase of blood urea four hours after a protein meal, which would make us feel that the

TABLE 8.—*Liver Function Tests in a Group of Miscellaneous Cases*

Name; Sex; Weight	Date	Changes in Blood Urea Nitrogen After Protein	Levulose Test, Bromsulphalein	Van den Bergh Test	Dye Test	Urine Urobilin	Diagnosis and Comment
E. M. F 20 Kg.	12/21/25	Fasting, 14.6 mg. 4 hours, 22.4 mg. Increase, 60%	.....	1:400,000	15 min. 5% 1 hour, 0	1:20 dilution	Leukopenic leukemia with large liver
P. D. M 34 Kg.	5/16/26	Fasting, 11.0 mg. 4 hours, 14.0 mg. Increase, 27%	.....	1:80,000	½ hour, 0	68 mg.	Hodgkin's disease with large liver
A. M. M 19 Kg.	4/30/26	Fasting, 15.4 mg. 4 hours, 19.6 mg. Increase, 28%	0.100 0.110 0.110 0.100 0.100	1:200,000	½ hour, 0	Absent	Abdominal tuberculosis (?) with large liver
A. D. M 22.5 Kg.	3/23/26	Fasting, 11.2 mg. 4 hours, 11.2 mg. Increase, 0	0.152 0.140 0.140 0.122	1:175,000	½ hour, 0	.....	Ketosis due to food poisoning; blood sugar 0.31 on admission and carbon dioxide, 30; after treatment with insulin and glucose, clinical recovery and normal function of liver attained
	3/30/26	Fasting, 11.2 mg. 4 hours, 19.6 mg. Increase, 75%	0.100 0.112 0.113 0.100	1:400,000	½ hour, 0		

enlarged liver meant liver injury. A patient with a severe case of ketosis showed a high fasting blood sugar with a practically normal levulose test, a slight increase of blood bilirubin and no increase in the blood urea four hours after the protein meal. After intensive insulin glucose therapy with forcing of fluids, the blood sugar returned to normal, the blood bilirubin reached its normal level and the protein meal caused a 75 per cent increase of the blood urea in four hours—all indicative of recovery from the previously diminished liver function.

In these cases of liver injury, we have noticed that the most constant and most positive indicator of hepatic hypofunction was the protein test. This was frequently corroborated by other tests for liver function that were simultaneously positive, and also by the fact that when the liver returned to normalcy, the protein test caused a normal increase in the

blood urea. In no case was a test for liver function undoubtedly positive when the protein test was normal. It may be worth noting that after the protein test, the best guide to liver injury was the van den Bergh test, then the dye test and the estimation of the urobilin in the urine, and last, the levulose test, which we found to be a poor test for liver function.

CONCLUSION

1. A new test for liver function is described, based on the normal conversion by the liver of amino-acids to urea.

2. After a protein meal of 1 Gm. per kilogram of weight, the blood urea will increase as the blood sugar does after a glucose meal. Normally the blood urea will increase at least from 50 to 70 per cent above the fasting level in four hours.

3. In cases of liver injury, this increase of the blood urea after a protein meal is much diminished, usually below 50 per cent, and sometimes an increase does not result in four hours.

4. Other tests for liver function have corroborated this test of subnormal hepatic function.

5. When the liver again becomes normal, the protein test also causes a normal increase in blood urea.

THE DIAMETER OF RED BLOOD CELLS IN HEALTH AND IN ANEMIA

A NEW METHOD OF MEASUREMENT *

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PITTSBURGH

It is an established fact that the average diameter of red blood cells in secondary anemia is decreased, and that many macrocytes are found in pernicious anemia. Occasionally there is difficulty in estimating the size of the cells by merely looking at the blood smear, especially if there is much distortion, or if the size and shape vary only slightly from normal. The exact measurement of the cells and the plotting of curves showing their distribution according to size may thus aid in the differentiation of anemias. My purpose was to find a practical and accurate method of measuring the diameter of the red blood cells.

Price-Jones [1] and others made stained films of blood, projected the image on to a sheet of paper, then measured the minimum and maximum diameters, and used the average as the diameter of the cell. In each film 500 cells were measured.

Grosh and Stifel [2] also used stained films, but measured the cells by means of a Leitz ocular micrometer. This is a glass disk which has a scale engraved on it, and which fits into the ocular of the microscope. The image of the scale focuses on the image of the blood film. The slide is moved by a mechanical stage, and only the round cells that happen to lie on the scale are measured.

TECHNIC

My method was to dilute the fresh blood with Hayem's solution, as in making a count of the red blood cells. The cells were thus measured in a moist preparation. Price-Jones [1] has shown that the diameter of the red blood cells in a dried film are smaller than the diameter of those in a moist preparation. I used a Bausch and Lomb Filar ocular micrometer to measure the diameters. As one looks into the ocular of the instrument, a vertical hair line is seen. This is a small wire that moves on a slide by means of a micrometer screw. Attached to the screw is a drum-head on which is a scale divided into fifty parts. The micrometer fits into the draw tube of the microscope and is secured by a set screw.

It is important that the apparatus be accurately calibrated, since there is too much error in depending on the theoretical magnification of the lenses. The instrument for this experiment was calibrated with an accurate stage micrometer

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* From the Medical Clinic, Mercy Hospital.

1. Price-Jones, Cecil: The Diurnal Variations in the Size of Red Blood Cells, J. Path. & Bact. **23**:71 (Dec.) 1920.

2. Grosh, L. C., and Stifel, J. L.: The Diameter of the Red Blood Cells in the Differentiation of Anemias, Arch. Int. Med. **36**:874 (Dec.) 1925.

obtained from the Bureau of Mines of this city and a Bausch and Lomb counting chamber. With the tube length of 160 mm. and using the high power lens, it was found that five divisions on the scale of the drum-head was equal to 1 micron. With the slide used in measuring the cells on the stage of the microscope, it was found that the tube length had to be changed to 170 mm. to give this reading. This final setting was checked by a Filar ocular micrometer from the Bureau of Mines. In all measurements the same apparatus was used. By means of the micrometer and a mechanical stage each cell can be individually measured accurately. Only round cells were measured, but no selection of these was made. In this way the one measurement served as the diameter of the red blood cell.

The normal curve was obtained by measuring the diameters of 2,000 red blood cells of ten normal persons. The average diameter was calculated, and the scale

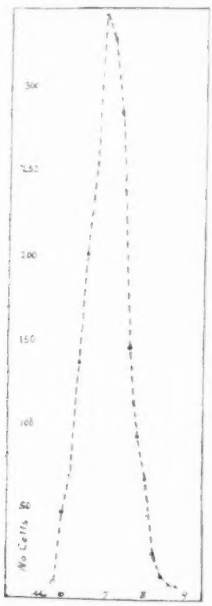

Chart 1.—Author's normal curve (2,000 cells); the average diameter was 7.32 microns.

was reduced to that of 200 and 100 cells. Usually 200 cells were measured, but it was found that a satisfactory curve for diagnosis could be obtained by estimating the size of 100 cells. The normal average diameter in this series was 7.32 microns. The average normal diameter as determined by Price-Jones was 7.21 microns; by Hampson and Shackle, 7.23 microns[3] and by Grosh and Stifel, 7.42 microns.[2]

NORMAL CURVE

The normal curve is symmetrical (chart 1). There is only one peak, which is well defined and which occurs at about the average diameter. The sides of the curve are almost straight lines. The difference between

3. Hampson, A. C., and Shackle, J. W.: Megalocytic and Nonmegalocytic Anemia, Guy's Hosp. Rep. **74**:193 (April) 1924.

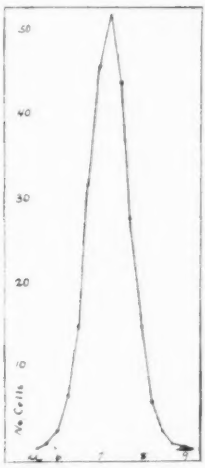

Chart 2.—Price-Jones normal curve (10,000 cells reduced to scale of 200 cells); the average diameter was 7.21 microns.

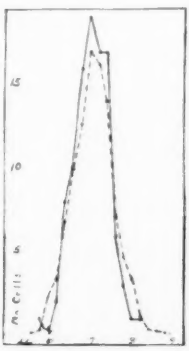

Chart 3

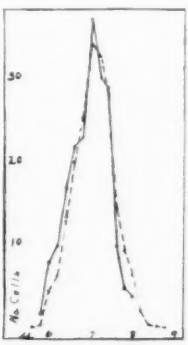

Chart 4

Chart 3.—Normal curve (100 cells); the average diameter was 7.103 microns. The broken line represents the author's normal curve; the average diameter was 7.32 microns.

Chart 4.—Normal curve (200 cells) the average diameter was 6.94 microns. The broken line represents the author's normal curve; the average diameter was 7.32 microns.

the smallest and the largest cell was only 3.2 microns, showing the slight normal anisocytosis. The normal curve as obtained by Price-Jones [1] (chart 2) closely resembles our normal curve. The individual normal curves approach the normal curve closely (charts 3 and 4), although the averages differ. The difference between the smallest (6.9 microns) and the largest (7.6 microns) individual normal average diameters was 0.7 micron.

SECONDARY ANEMIA

The curve of secondary anemia is somewhat asymmetrical, but not to a marked degree (charts 5, 6 and 7). It is found to the left of the normal curve. The average diameter is smaller than normal. There is

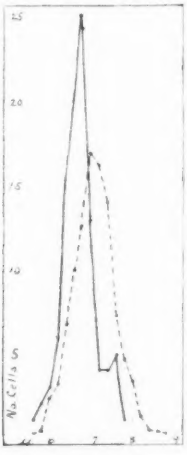

Chart 5.—Secondary anemia (cancer of stomach); the average diameter of 100 cells was 6.72 microns. The broken line represents the author's normal curve; the average diameter was 7.32 microns.

usually only one peak, and it is almost as well defined as normal. In the present series the variation in the size of the cells was usually less than normal, but it may be greater.

PERNICIOUS ANEMIA

The curve of pernicious anemia is asymmetrical. The greater part of the usual curve lies to the right of the normal curve (chart 8). The average diameter is greater than normal. The curve is flattened out, there being many peaks. The anisocytosis is marked, and the degree varies in general directly with the anemia; but there is no relation between the average diameter and the degree of variation.

In a few of the cases of pernicious anemia which I measured, a different type of curve was obtained. These cases were of an acute type with red cell counts below one million, although not all the cases with so severe an anemia showed this type of curve. The curve is low and spread out, even more so than is usual in pernicious anemia; but it lies to the left of the normal curve. The average diameter is below normal. There were no large irregular cells in this type, all the cells being small and round or oval. In one case (chart 9) not one macrocyte was seen. Clinically these were typical cases of pernicious anemia. The toxin was so severe that it produced degenerative changes in the bone marrow, so that only cells that were small and poor in hemoglobin were formed. Thus, according to these observations, the

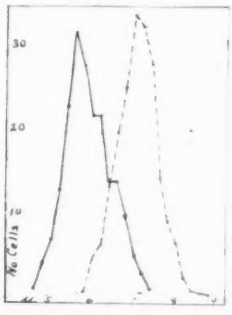

Chart 6

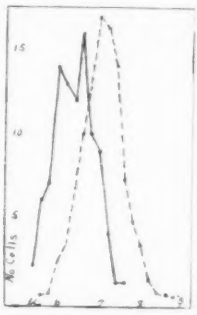

Chart 7

Chart 6.—Secondary anemia; the average diameter of 200 cells was 5.90 microns. The broken line represents the author's normal curve; the average diameter was 7.32 microns.

Chart 7.—Secondary anemia (chlorosis); the average diameter of 100 cells was 6.39 microns. The broken line represents the author's normal curve.

differentiation of the anemias cannot be based entirely on the average diameter but on the type of curve found, that is, on the distribution of the cells according to size.

The typical curve of pernicious anemia, as first described, was also found in one case during a remission (chart 10). The patient was receiving the usual treatment. There is usually less anisocytosis at this time than during the active stage of the disease.

The megalocytic type of curve has been reported as occurring in sprue,[4] infantilism [3] and *Bothriocephalus latus* infestation.[4]

4. Hampson, A. C., and Shackle, J. W. (footnote 3). Passey, R. D.: Measurements of the Red Blood Cells in the Anemias of Sprue and Debothriocephalus Latus Infection, Guy's Hosp. Rep. **74**:329 (July) 1924.

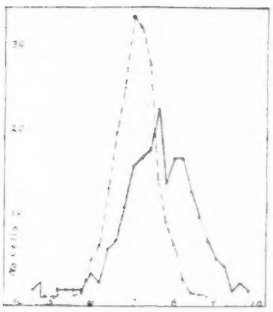

Chart 8

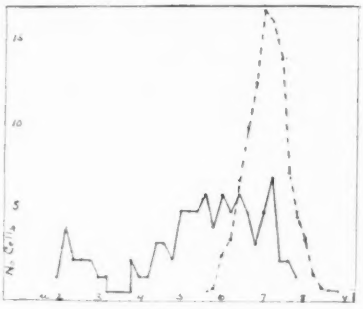

Chart 9

Chart 8.—Pernicious anemia (1,200,000 red blood cells); the average diameter of 200 cells was 8.12 microns. The broken line represents the author's normal curve.

Chart 9.—Pernicious anemia (500,000 red blood cells); the average diameter of 100 cells was 5.45 microns. The broken line represents the author's normal curve.

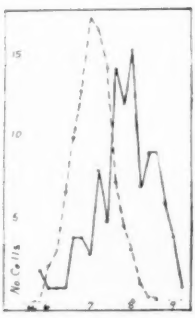

Chart 10

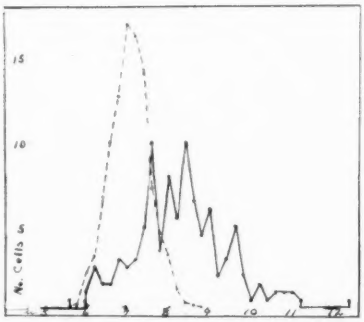

Chart 11

Chart 10.—Pernicious anemia remission (80 per cent, 4,100,000); the average diameter of 100 cells was 7.76 microns. The broken line represents the author's normal curve.

Chart 11.—Pernicious anemia (2,810,000 red blood cells) before treatment, July, 1926. The average diameter of 200 cells was 8.34 microns. The broken line represents the author's normal curve.

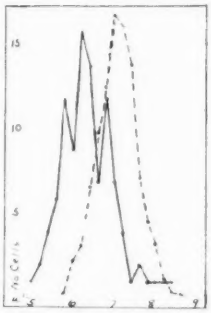

Chart 12

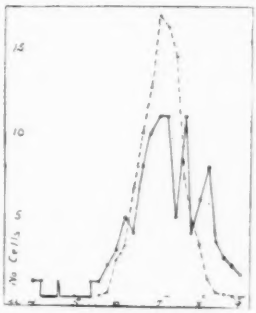

Chart 13

Chart 12.—Pernicious anemia (3,720,000 red blood cells) after treatment, October, 1926. Average diameter of 100 cells was 5.84 microns. The broken line represents the author's normal curve.

Chart 13.—Pernicious anemia (1,000,000 red blood cells) before treatment, Sept. 27, 1926. The average diameter of 100 cells was 7.94 microns. The broken line represents the author's normal curve.

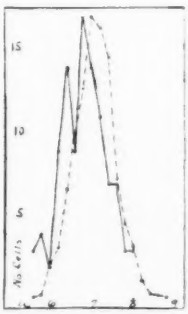

Chart 14

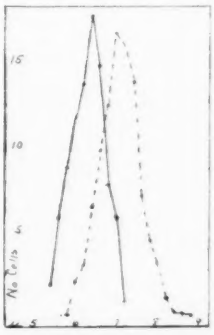

Chart 15

Chart 14.—Pernicious anemia (2,650,000 red blood cells) after treatment, Oct. 14, 1926. The average diameter was 6.94 microns. The broken line represents the author's normal curve.

Chart 15.—Pernicious anemia (2,700,000 red blood cells) after treatment, Nov. 12, 1926. The average diameter of 90 cells was 6.3 microns. The broken line represents the author's normal curve.

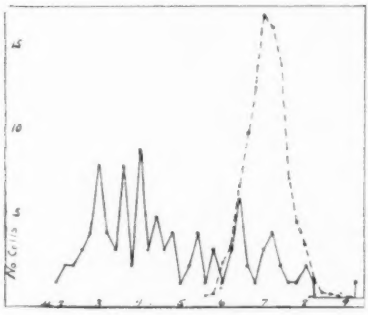

Chart 16.—Pernicious anemia (900,000 red blood cells) before treatment, April, 1926. The average diameter of 100 cells was 4.74 microns. The broken line represents the author's normal curve.

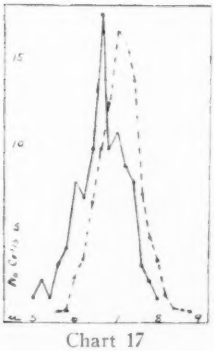

Chart 17

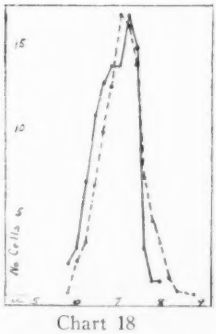

Chart 18

Chart 17.—Pernicious anemia (2,800,000 red blood cells) after treatment, May, 1926. The average diameter of 100 cells was 6.65 microns. The broken line represents the author's normal curve.

Chart 18.—Pernicious anemia (4,100,000 red blood cells) after treatment, Aug. 12, 1926. The average diameter of 100 cells was 6.88 microns. The broken line represents the author's normal curve.

An interesting change occurred in the curves of pernicious anemia in those cases in which the patients had been treated by the liver diet according to Minot and Murphy.[5] Both types of curves assumed a form resembling that found normally or in secondary anemia. The average diameter that was larger than normal became smaller than normal. Early in the treatment the curve was still asymmetrical (charts 11 and 12) but moved to the left of the normal curve, whereas formerly it was, in great part, on the right; this is due to the disappearance of the macrocytes. Later in the course of the treatment, the curve became symmetrical (charts 13, 14 and 15). In the type of pernicious anemia in which the average diameter was smaller than normal, it became larger, but still less than normal (charts 16, 17 and 18). In the case illustrated by chart 18 the curve closely approaches normal. The curves showing the change under the treatment outlined by Minot and Murphy are to be contrasted with those in the case previously shown in remission (chart 10) in which the usual method of treatment was used. Not all cases respond to the liver diet. In one case, a typical curve of pernicious anemia persisted up to the time of death, in spite of the treatment.

CONCLUSIONS

1. A practical and accurate technic has been described for measuring the diameter of the round red blood cells.

2. The measurement of the cells and plotting of the curves are frequently of great diagnostic value.

3. The curves in normal cases and those in cases of secondary anemia are characteristic and constant.

4. In pernicious anemia two types of curves were found.

5. The average diameter is not always increased in pernicious anemia.

6. Treatment of patients with pernicious anemia by the method described by Minot and Murphy produces definite changes in the size of the red blood cells.

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5. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

CEREBROSPINAL FLUID IN NEPHRITIS *

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AND
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ASSISTED BY JOHN E. HEARN
NEW YORK

It seems fair to say that the increasing difficulty in the diagnosis of cases with cerebral, or rather central nervous system, manifestations has not been lessened by the increased data concerning epidemic encephalitis and its bizarre symptomatology. One cannot help but feel that the recognition of this feature of encephalitis has led in great measure to a certain laxness in following puzzling cases to a definite conclusion.

Discussion as to the ultimate diagnosis in one fatal case gave rise to the question whether an apparently noninflammatory condition of the central nervous system could produce a spinal fluid like that in epidemic encephalitis or in other inflammatory conditions. Is increased protein (albumin and globulin) in the cerebrospinal fluid always a sign of inflammation? Could chronic nephritis with uremia, a supposedly non-inflammatory condition in relation to the central nervous system, account for a similar picture?

Baar [1] studied the diagnostic value of increased globulin in spinal fluids, particularly in diseases of children, and noted the presence of an increase in uremia. He noted that the increase in protein was so marked as to suggest tuberculous meningitis. Alpers [2] reviewed the literature, compiling ninety-eight cases. We shall refer to this review in the course of this article. No attempt to establish a definite picture for the cerebrospinal fluid in chronic nephritis has previously been made, and little work has been performed particularly in reference to the protein content.

We have had the opportunity to study the cerebrospinal fluid in twenty-two cases of nephritis.

METHODS

The determinations of sugar in blood and in cerebrospinal fluid were made by Folin's method,[3] but in preparing the protein-free filtrate from spinal fluid

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1. Baar, H.: The Diagnostic Value of Increased Globulin of the Spinal Fluid in Affections of Children, Wien. klin. Wchnschr. **34**:614, 1921.

2. Alpers, B. J.: Human Cerebrospinal Fluid in General System and Metabolic Diseases, J. Nerv. & Ment. Dis. **62**:265 (Sept.) 1925.

3. Folin, O.: J. Biol. Chem. **38**:98, 1919.

one-fourth the usual quantities of 10 per cent sodium tungstate and two-thirds normal sulphuric acid were used, and the final dilution was 1:5 instead of 1:10, as in blood. For nonprotein nitrogen in blood the usual 1:10 filtrate and in spinal fluid the 1:5 filtrate were employed. The method of Folin and Wu[4] was followed. The method adopted for uric acid was that of Folin[5] with the improved reagent.[6] The procedure of Folin and Wu[7] was followed for preformed creatinine.

Total nitrogen in spinal fluid was determined by a modification of the procedure of San Yin Wong,[8] hydrogen peroxide as suggested by Rose[9] being used instead of potassium persulphate. Occasionally the work was checked with the macro-Kjeldahl method.

The difference between the nonprotein nitrogen content and the total nitrogen when multiplied by 6.25 was taken as the protein content. This calculation seems to be more accurate when the nonprotein nitrogen is not excessively high. An example will make this clear. In one case the total nitrogen was 18 mg. and the nonprotein nitrogen, 10 mg.; the protein content was 50 mg. In another case the total nitrogen was 216 mg. and the nonprotein nitrogen 200 mg.; the protein content was taken to be 100 mg. It is obvious that the error is much greater in the second case when one realizes that a hardly perceptible turn of the colorimeter screw will not make any difference in the first case, but an immense difference in the second. When it is necessary to dilute the cerebrospinal fluid for the estimation of nitrogen, it is apparent that the error is in proportion to the dilution factor; and as the proportion of the various proteins is not constant in different fluids, it is apparent that an unknown error exists in the usual protein nitrogen factor, 6.25. An error of one division on the colorimeter vernier gives an error for the first case mentioned of approximately 2 per cent of protein. The same error for the second case, the cerebrospinal fluid being diluted 1:10, amounts to 6 per cent. This is without reckoning errors of dilution and other factors in the estimations of the nonprotein nitrogen. Supposing, however, that the nonprotein nitrogen in the second case were 16 mg.; the protein would be 1250, and an error of one division on the vernier would reduce the protein figure to 1,244, a negligible error of 6 mg. in 1,250, or less than 0.5 per cent.

Van Slyke's method[10] was used for chlorides in blood plasma and in cerebrospinal fluid. To determine the presence of albumin qualitatively the nitric acid ring test was used, and for globulin the Pandy reaction.

CEREBROSPINAL FLUID IN NEPHRITIS

The fluid in all cases was clear and, with one exception, colorless. In the exception, there was a faint yellow-green tinge. For obvious reasons, blood contaminated fluids are not included in this study.

Manometer readings were not taken, but in the majority of cases the pressure was increased as judged by the initial spurt from the needle and the rapidity of flow.

The cell count varied from 2 to 16 cells per cubic millimeter, all lymphocytes except in one case in which, with a count of 14, 50 per cent

4. Folin and Wu: J. Biol. Chem. **38**:81, 1919.
5. Folin, O.: J. Biol Chem. **54**:153 (Oct.) 1922.
6. Folin, O. and Trimble, H.: J. Biol. Chem. **60**:473 (June) 1924.
7. Folin and Wu: J. Biol. Chem. **38**:81, 1919.
8. San Yin Wong: J. Biol. Chem. **55**:431 (March) 1923.
9. Rose, A. R.: J. Biol. Chem. **64**:253 (June) 1925.
10. Van Slyke: J. Biol. Chem. **58**:523 (Dec.) 1923.

were polymorphonuclears. In six, or 21 per cent, the count was higher than 10. (The presence of uremic symptoms has no relation to the cell count, nor, apparently, has the type of nephritis which is encountered.)

CHEMISTRY

Sugar.—All fluids gave a reduction with Benedict's solution. The amount of sugar varied from 31 to 125 mg. per one hundred cubic centimeters. If we take 70 mg. as the upper normal value for cerebrospinal fluid sugar, then twelve, or 50 per cent, of the cases were higher than normal; only one fluid gave a low value, 31 mg.

In cases of chronic nephritis only, the average cerebrospinal fluid sugar was 82.8 mg. for cases with uremic symptoms and 57.2 mg. for those without uremic manifestation.

Normally, the ratio, $\frac{\text{Cerebrospinal fluid sugar}}{\text{Blood sugar}}$, varies from 40 to 65 per cent. In eleven of our cases, or 50 per cent, the ratio is high, averaging 74.3 per cent. In one case identical values were obtained for blood and cerebrospinal fluid, and in one case as low a ratio as 26 per cent was found. Except in tuberculous meningitis, we have never seen such a low ratio in a clear fluid.

The chlorides range from 562 to 807 mg. per one hundred cubic centimeters, excluding postmortem fluids. The upper normal value is 750 mg. In nine, or 37.5 per cent of our cases, the chlorides were high, averaging 779 mg. The blood plasma chlorides in these cases were, with two exceptions, above the high normal of 590 mg. per one hundred cubic centimeters.

Postmortem fluids excluded, the average amount of chlorides in cases of chronic nephritis is 727.5 mg. for those with uremic manifestations and 784 for those without. The amount of chlorides was low in two cases, 562 and 620 mg. In these the blood plasma chlorides were also low, being, respectively, 362 and 421 mg. per one hundred cubic centimeters. In three cases low blood plasma chlorides, 538, 491 and 527 mg., were present with normal cerebrospinal fluid chlorides.

In fluids taken post mortem, the chlorides are exceptionally high—in one case 825 mg. in a fluid drawn five minutes post mortem and 960 mg. in a fluid drawn one hour after death.

Comment.—Cerebrospinal fluid chlorides in chronic nephritis are generally not increased. Our figures show a value somewhat higher than normal for cases without uremic symptoms, namely, 784 mg.

It is noteworthy that the cerebrospinal fluid chlorides in our cases of chronic nephritis with edema are especially the same as in those without edema, being 746 mg. per one hundred cubic centimeters in the former and 743 mg. in the cases without edema. Mestrezat,[11]

11. Mestrezat, W.: Le liquide cephalo-rachidien, Paris, A. Maloine, 1912.

Levinson,[12] and Boyd,[13] however, report higher figures for cerebrospinal fluid chlorides in chronic nephritis with edema. Their values range from 0.8 to 0.85 per cent (800-850 mg.).

Nonprotein Nitrogen.—The nonprotein nitrogen ranged from 8 to 210 mg. per one hundred cubic centimeters, and excluding the cases of acute nephritis, from 15 to 210 mg. In cases with uremic symptoms in which there was retention of nitrogen in the blood, the cerebrospinal fluid nonprotein nitrogen averaged 121 mg.; in nonuremic cases with retention of nitrogen, 90.6 mg.

The ratio, $\frac{\text{Cerebrospinal fluid nonprotein nitrogen}}{\text{Blood nonprotein nitrogen}}$, when there is not a retention of nitrogen, is 46 per cent. In this series the ratio in the presence of retention of nitrogen is 80 per cent.

Protein.—Qualitative studies alone show a definite increase in albumin and globulin in the cerebrospinal fluid in cases of chronic nephritis. Acute nephritis, unless accompanied by uremic symptoms, does not show an increase. The quantitative observations agree closely with the qualitative determinations.

The normal cerebrospinal fluid protein content ranges from 20 to 50 mg. per one hundred cubic centimeters. The average protein content of all cases of chronic nephritis is 127 mg.; of those cases with uremic symptoms the average is 133 mg.; nonuremic cases show 111 mg. protein per one hundred cubic centimeters. There is, then, a marked increase in the protein content of cerebrospinal fluid in chronic nephritis, higher figures being obtained when uremic symptoms are present. With two exceptions, all patients having over 100 mg. protein in the cerebrospinal fluid died. These two patients, one with 138 mg. and the other with 119 mg., left the hospital definitely unimproved and gravely ill. The outcome is unknown.

We must reiterate here what was pointed out in the discussion of the methods employed in this study. Though there is a definite and undoubted increase in the protein in the cerebrospinal fluid in cases of chronic nephritis, the quantitative protein figures must at this time be accepted more for their relative than for their absolute values, owing to the nature of the methods perfected to date.

Comment.—Alpers,[2] after studying the literature, concludes that "in uremia the spinal fluid changes are different from those in nephritis." On the basis of our study, what exists is not so much a difference in the observations grossly, but rather one of degree, depending on the severity of the condition. An attempt has not been made in this study to follow the "pure" and "secondary" or "associated" uremia classification of

12. Levinson, A.: Cerebrospinal Fluid in Health and Disease, St. Louis, C. V. Mosby Company, 1923.

13. Boyd, W.: Physiology and Pathology of the Cerebrospinal Fluid, New York, MacMillan, 1920.

Mollard and Froment.[14] We have used the term uremia in its broad sense to denote those cases of chronic nephritis in which coma, lethargy, convulsions, twitchings or persistent vomiting have been prominent features.

On this basis our data are not directly comparable to Alpers' study. It is noteworthy, however, that although in his cases of "associated" or "secondary" uremia (namely uremia with demonstrable etiology according to Mollard and Froment) "the albumin content is qualitatively normal," all our patients with uremic symptoms showed an increase in the albumin as well as in the globulin content.

It is interesting to speculate on the origin of the increased albumin and globulin in the cerebrospinal fluid in cases of nephritis. The choroid plexus has been thought to act as a barrier between the blood and the subarachnoid fluid. This plexus, with its permeability intact, is able, it is thought, to maintain a cerebrospinal fluid of fairly uniform composition. It is the injury to this barrier, as a result of retained or elaborated toxins due to the nephritic disturbance, that is thought to account for the changes in the cerebrospinal fluid in chronic nephritis. Monakow[15] extirpated the kidneys in rabbits and found what he described as a more or less typical vacuolization of the epithelial cells of the choroid plexus. Our mercuric case with the history of having swallowed mercuric chloride did not show any of these changes in the choroid plexus at autopsy.

Our figures show also that there is not a relationship between the amount of protein in the cerebrospinal fluid and the blood pressure, either systolic or diastolic. The presence of an increased amount of sugar in the cerebrospinal fluid in chronic nephritis (50 per cent of this series) as well as in encephalitis adds to the difficulty of diagnosis.

Whatever the theoretical considerations, from a clinical standpoint it is important to remember that the presence of increased protein in the cerebrospinal fluid can no longer be considered as the result of a purely inflammatory process in relation to the central nervous system. It is not unreasonable to suppose that some obscure cases with symptoms of the central nervous system caused by uremia have possibly been termed cases of atypical encephalitis because of the increase in protein.

CEREBROSPINAL FLUID IN ACUTE INFECTIOUS NEPHRITIS

Acute Nephritis.—As only three cases are included in this study, the observations must be accepted with the reservations necessarily attendant on any conclusions drawn from so small a number. Nevertheless, the observations are of interest and are presented here for the value attached to them as part of the study of cerebrospinal fluid in nephritis.

14. Mollard and Froment: Urea dans le liquide cephalo-rachidien et uremie nerveuse. J. de physiol. et de path. gén. **2**:263, 1909.

15. Monakow, P.: Uremia and Choroid Plexus. Schweiz. Arch. f. Neurol. u Psychiat. **13**:11, 1923.

	Age	Sex	Nonprotein Nitrogen: Blood	Nonprotein Nitrogen: Spinal Fluid	Nonprotein Nitrogen: Spinal Fluid Blood, %	Sugar: Blood	Sugar: Spinal Fluid	Sugar: Spinal Fluid Blood, %	Chlorides: Blood	Chlorides: Spinal Fluid	Chlorides: Spinal Fluid Blood, %	Blood: Uric Acid	Blood: Creatinine	Blood: Wassermann Reaction	Spinal Fluid: Wassermann Reaction	Spinal Fluid: Cells	Spinal Fluid: Qualitative: Albumin	Spinal Fluid: Qualitative: Globulin	Spinal Fluid: Qualitative: Sugar	Spinal Fluid: Protein	Spinal Fluid: Colloidal Gold	Urine: Albumin	Urine: Casts	Maximum Blood Pressure	Eye-ground Changes	Convulsions: Coma	Convulsions: Convulsions	Edema	
Chronic Nephritis with Nitrogen Retention and Edema																													
1	33	F	210	210	100	163	116	71	530	737	139	11.4	14.0	Neg.	Neg.	14 {7P} {7L}	+++	+++	++	94	0001110000	++	0	154/ 70	0	+	0	++	Died 1 day after puncture
2	47	M	200	166	83	111	87	78	608	(825)	135	11.6	12.0	Neg.	Neg	4 L	+++	++	+	212	0012210000	.....	.....	190/ 70	Cataracts	0	+	+	Puncture done 5 minutes post mortem
3	26	M	200	168	84	111	79	71	538	737	137	3.2	23.0	Neg.	.....	6 L	+++	++	++	200	.....	+++	G.	180/120	+	Terminal	0	+++	Died 10 days after puncture
4	10	M	76	61	80	95	53	56	597	749	123	7.5	3.0	.....	.....	....	+	+	+	75									
			178	154	86	121	87	72	585	(807)	138	16.0	8.6	Neg.	.....	11 L	+++	++	+	131	.....	++++	G.H.	168/110	+	+	+	+++	Died
5	26	M	143	105	73	98	56	57	608	807	133	....	....	Neg.	Neg.	11 L	++	++	+	100	0001210000	++++	0	191/122	+	0	0	++	Died
6	21	M	125	89	71	93	51	55	608	784	129	6.0	13.3	Neg.	Neg.	7 L	++	++	+	100	0000000000	+++	G.H.	170/112	+	0	0	+++	Home; unimproved
7	33	M	120	118	98	97	63	65	597	796	133	3.4	....	Neg.	Neg.	7 L	++	++	+	138	0000000000	++++	G.H.	165/115	0	0	0	+++	Home; unimproved
8	30	F	115	80	69	97	57	58	608	772	127	6.0	2.5	Neg.	Neg.	4 L	++	+	+	100	0000110000	+++	G.	120/120	+	0	0	++	Home; improved
9	90	M	80	57	71	120	82	68	679	807	119	5.3	....	.....	Neg.	3 L	++	++	+	144	0012210000	+++	H.	.....	Cataracts	+	0	+	Died day of puncture
10	55	M	70	38	54	175	125	71	585	760	130	3.2	1.8	Neg.	Neg.	4 L	++	++	+	131	0001110000	+++	G.H.	110/ 80	0	+	0	+++	Died 9 days after puncture
Chronic Nephritis with Nitrogen Retention; Edema Not Present																													
11	52	M	256	190	71	106	87	82	620	(960)	155	16.7	4.3	Neg.	Neg.	16 L	+++	++	+	200	0000000000	++	0	94/ 60	.....	0	0	0	Puncture done 1 hour post mortem; complicated with auricular fibrillation and aphasia
12	40	M	154	133	86	100	65	65	608	772	127	6.6	....	Neg.	a/c	2 L	+++	+	+	169	0001110000	++++	G.	220/130	+	0	Local tremors	0	Died 4 days after puncture
13	30	M	125	87	70	108	108	100	491	685	139	20.0	9.2	Neg.	Neg.	12 L	++	++	+	188	0000000000	++++	G.H.	155/ 80	+	+	+	0	Died 1 day after puncture
14	39	M	70	67	96	100	75	47	556	755	136	4.4	....	Neg.	.....	6 L	+	+	++	62.5	0001100000	++	All G.	140/100	+	Stuporous	+	0	Home; improved
15	65	M	84	61	73	97	59	61	603	760	125	7.3	....	Neg.	.....	4 L	+++	++	+	119	0012210000	+	G.H.	210/120	+	0	0	0	Home; unimproved
Chronic Nephritis with Edema: No Nitrogen Retention																													
16	38	F	47	37	79	117	71	61	362	562	155	2.5	2.8	.....	.....	2 L	+	++	+	97	.....	+							
			29	15	52	91	63	69	527	690	131	....	....	Neg.	Neg.	3 L	+	+	+	81	0000000000	.....	All H.	118/ 78	.....	Stuporous	0	+	Home; improved
17	41	F	35	20	57	90	61	68	608	749	123	....	....	Neg.	Neg.	2 L	+	+	+	75	0000000000	++++	All G.	288/188	+	+	0	+	Home; improved
Acute Nephritis																													
18	3 mo.	F	23	8	34	100	64	64	573	690	120	2.0	....	++++	a/c	7 L	+	+	+	25	0000000000	++++	G.H.	.....	.....	.....	0	+	Died of pneumonia; congenital syphilis
Acute Nephritis, Uremia																													
19	38	M	31	17	55	100	67	67	573	749	131	5.4	2.3	Neg.	Neg.	15 L	+	+	+	75	0000000000	++++	G.H.	170/110	0	Stuporous	0	+++	Home; improved
Acute Nephritis																													
20	3	M	40	22	55	108	68	63	562	725	129	4.7	2.4	Neg.	Neg.	4 L	+	+	++	36	.....	+++	G.H.	120/ 85	0	0	0	+	Discharged improved
Nephritic Toxemia of Pregnancy																													
21	31	F	40	20	50	118	31	26	608	749	123	5.2	1.7	.....	.....	.....	++	+++	++	175									
			75	59	78	210	94	45	608	(796)	131	7.6	4.0	Neg.	Neg.	8 L	+++	+++	+++	81	2221110000	++++	G.H.	260/150	+	+	+	+++	Died; second puncture made directly post mortem
Mercuric Chloride Poisoning																													
22	36	M	170	143	84	192	125	65	421	620	147	8.0	10.0	Neg.	Neg.	4 L	+	+	+++	119	0000000000	qns.	qns.	160/ 80	0	+	0	0	Died 7 days after ingestion

In this table a/c means anticomplementary; P, polymorphonuclears; L, lymphocytes; G., granular; G.H., granular and hyaline; H., hyaline; qns., not sufficient quantity.

The fluid in every case was clear and under normal pressure. The cell counts were 7, 4 and 15 cells, respectively, all lymphocytes.

The cerebrospinal fluid nonprotein nitrogen was normal and bore the normal relationship to the blood nonprotein nitrogen, averaging 48 per cent. Attention must be called to the fact that in none of our cases of acute nephritis was there any retention of nitrogen.

The cerebrospinal fluid sugar averaged 66 mg., or 65 per cent of the blood sugar.

The chloride content was normal, our figures being 690, 749, and 725 mg. per one hundred cubic centimeters, averaging for all three cases 126 per cent of the blood plasma chlorides.

Only the case with the uremic symptoms showed an increase in protein, having 75 mg. per one hundred cubic centimeters. The other two were normal, being 25 and 36 mg., respectively.

Comment.—Judged on the basis of the few cases studied, the cerebrospinal fluid in uncomplicated acute nephritis is normal. The protein content both qualitatively and quantitatively is normal except when uremic manifestations are present. In case 19, the patient was markedly stuporous at the time of the lumbar puncture, and the fluid showed an increase in protein. Leopold and Bernard[16] report two cases of acute nephritis in children, one with uremic symptoms. The cerebrospinal fluid of this case did not show an increase in globulin, but the cell count was high, 60.

We wish to discuss two of our cases separately, as they cannot, with any definiteness, be placed in any of the more usual classifications.

REPORT OF CASES

Toxemia of Pregnancy with Nephritis.—E. R., a colored woman, aged 31, a tertiodecipara, who was admitted to the obstetrical service April 7, 1926, as nonurgent, complained chiefly of headache, and the appearance of spots before the eyes during the past few weeks.

The patient had had trouble with most of the previous pregnancies, requiring surgical intervention before full term. One year ago, when thirty weeks pregnant, she had had a condition similar to that for which she now was admitted.

The physical examination showed a stout colored woman, somewhat dyspneic, not acutely ill, and not in labor. The heart was enlarged to the left; the lungs were normal; pregnancy was of about six months' duration; the blood pressure was systolic 270, and diastolic 150; both disks were blurred.

She suddenly developed convulsions, went into coma and failed to rally despite stimulation. The blood pressure dropped from 270 systolic and 150 diastolic to 76 systolic and 44 diastolic some hours before death, which occurred about thirty hours after admission.

The cerebrospinal fluid was clear, under increased pressure, and contained a normal number of cells. Protein in the first puncture was definitely increased, being 175 mg. per one hundred cubic centimeters and falling to 81 in the postmortem cistern fluid. In addition to the increased protein, the outstanding feature

16. Leopold and Bernard: Chemistry of Spinal Fluid, Am. J. Dis. Child. **13**:34 (Jan.) 1917.

was the exceedingly low cerebrospinal fluid sugar, 31 mg., which was only 26 per cent of the blood sugar. To our knowledge, this low percentage in a clear fluid has been reported previously only in tuberculous meningitis. The colloidal gold curve, 2,221,110,000, of itself is suggestive of a pathologic change in the central nervous system, but the blood and cerebrospinal fluid negative Wassermann reactions tend to rule out, though not definitely, of course, any specific infection as the underlying factor.

Mercuric Chloride Poisoning.—A. D., aged 36, entered the hospital March 11, 1926, with the history of having swallowed mercuric chloride (one-half teaspoonful of powder in water). He soon became nauseated and vomited. His stomach was lavaged shortly afterward. He had not had any cardiorespiratory condition or nocturia (measles and diphtheria in infancy). The patient was sitting up comfortably in bed; the pupils were equal and reacted to light; the edges of the gums were bluish and slightly reddened; there was no edema; the knee reflex was present.

The patient had almost complete anuria from the very onset and failed to rally despite the administration of sodium thiosulphate in gram doses daily, intravenously, and daily colonic irrigations. He died six days after admission.

On March 16, a spinal puncture showed a marked increase in nonprotein nitrogen and sugar, but the amount of chlorides was normal. The protein content was 119 mg., a definite increase. The cell count was normal.

Autopsy.—Autopsy showed the typical gross kidney observations of mercuric chloride poisoning—violaceous pyramids and swollen cortex; ulcerative colitis was present. The brain was normal. Microscopically there was an acute tubular degenerative nephritis with marked congestion and the presence of calcification in the tubules.

COLLOIDAL GOLD

The number and variety of causes assigned to the mechanism of the colloidal gold reaction attest our lack of accurate knowledge regarding it. It has been shown (Weston quoted by Warwick and Nixon [17]) that the substance is dialyzable through membranes impermeable to albumins and is precipitated by ammonium sulphate; hence, a globulin. On the other hand, pathologic increase in albumin has been said by another observer to be the cause of the precipitation. Still other workers have regarded it as a physical phenomenon, probably of electrical nature.

From our colloidal gold readings, it appears that proteins per se, that is, albumin and globulin, do not produce precipitation of the colloidal gold suspension. Two outstanding cases, 8 and 9, show at once the presence of completely negative colloidal gold reactions with quantitative protein values of 200 and 188 mg., respectively.

On the whole, a characteristic change in the colloidal gold curve of the cerebrospinal fluid in nephritis is not apparent.

The dearth of autopsy material in this article is greatly regretted. Clinical work can never have the value of clinicopathologic observations. We feel, however, that the cases described in this article are for the most part clear-cut clinical pictures recognized by all as nephritis.

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17. Warwick and Nixon: Study of Colloidal Gold Reaction and Its Clinical Interpretation, Arch. Int. Med. **25**:119 (Feb.) 1920.

CONCLUSIONS

1. Cerebrospinal fluid and blood studies were made on cases of nephritis with and without uremic manifestations.

2. The cerebrospinal fluid in chronic nephritis shows the following:

(*a*) The cerebrospinal fluid is clear. This was true in all of our cases except one, in which the fluid had a faint yellow-green tinge. Pressure, as judged by the initial spurt and rapidity of flow, is increased.

(*b*) The cell count varies from 2 to 16 per cubic millimeter; these cells are essentially all lymphocytes. With the exception of one case with a polymorphonuclear count of 50 per cent, this was true in the series studied. The presence of uremia has no relation to the cell count.

(*c*) The nonprotein nitrogen of the cerebrospinal fluid is increased and is higher than the normal proportion in relation to the blood nonprotein nitrogen. The ratio, $\frac{\text{Cerebrospinal nonprotein nitrogen}}{\text{Blood nonprotein nitrogen}}$, normally 46 per cent, rises to 80 per cent in the presence of nitrogen retention.

(*d*) The chlorides are not generally increased. The figures for the cases with edema are essentially the same as for those without edema. In fluids taken post mortem the chlorides are exceptionally high.

(*e*) There is a definite increase in albumin and globulin in cases of chronic nephritis; the highest figures are obtained in the presence of uremia. When the protein is more than 100 mg. per one hundred cubic centimeters, the prognosis is grave.

(*f*) The ratio, $\frac{\text{Blood sugar}}{\text{Cerebrospinal fluid sugar}}$, is higher in chronic nephritis, averaging 74.3 for eleven of our cases. Over 50 per cent of the cases gave a higher cerebrospinal fluid sugar than normal. In the presence of uremia the average figure obtained is higher than in the absence of uremia.

3. In the absence of uremic manifestations, the cerebrospinal fluid in acute nephritis is essentially normal in all respects. In the presence of uremic symptoms, the protein content rises.

4. In the acute nephritis of mercuric chloride poisoning, the cerebrospinal fluid resembles closely that seen in chronic nephritis.

5. Apparently there is not a characteristic change in the colloidal gold curve of the cerebrospinal fluid in nephritis. The amount of protein per se, that is, albumin and globulin, bears no direct relation to precipitation of the colloidal gold suspension.

THE TOXIC ACTION OF CYSTINE ON THE KIDNEY*

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It has been shown by Newburgh and his collaborators [1] that diets high in protein are injurious to the kidneys. In the attempt to explain the mechanism of this injury it was found that the intravenous injection of certain amino-acids into animals gave positive results,[2] and that the injury produced was obtained by a single dose or, at most, by the administration of a few doses of the amino-acid in question.

These acute lesions caused by large intravenous doses suggest the possibility that the introduction of the amino-acid into the body in small doses with the food over a long period of time might also produce injury. This investigation was devised to obtain an answer to this question.

Cystine was selected as the amino-acid to be studied in this regard for several reasons: 1. When it is injected intravenously,[2] a severe lesion is produced. 2. Cystine is an essential amino-acid, as Mendel [3] has shown. He demonstrated this fact by feeding a cystine-poor ration, obtained by using casein as the protein and by restricting it to 8 per cent of the diet. On this diet, growth is limited by the small amount of cystine present. Mendel [3] has further shown that the addition of 0.25 per cent cystine to this diet promotes growth. It is therefore possible to determine, by graded additions of cystine to such a casein diet, at what level (if any) beyond the requirement for growth the cystine of the diet may become harmful to the kidneys. 3. Lignac [4] has reported

* From the Department of Internal Medicine, University of Michigan Medical School.

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1. Newburgh, L. H.: Production of Bright's Disease by Feeding High Protein Diets, Arch. Int. Med. **24**:259 (Oct.) 1919. Newburgh, L. H., and Clarkson, Sarah: Renal Injury Produced in Rabbits by Diets Containing Meat, Arch. Int. Med. **32**:850 (Dec.) 1923. Newburgh, L. H.; Marsh, P. L.; Clarkson, Sarah, and Curtis, A. C.: The Dietetic Factor in the Etiology of Chronic Nephritis, J. A. M. A. **85**:1703 (Nov. 28) 1925.

2. Newburgh, L. H., and Marsh, P. L.: Renal Injuries by Amino-Acids, Arch. Int. Med. **36**:682 (Nov.) 1925.

3. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **17**:325, 1914; **20**:351, 1915.

4. Lignac, G. O. E.: Krankheitsforschung **2**:43, 1925.

severe tubular injury in mice caused by the subcutaneous injection of a suspension of cystine. 4. H. B. Lewis [5] has found that the introduction of cystine into the body of rabbits through the digestive tract is nephrotoxic when the doses are large. He introduced a suspension of cystine into stomachs of fasting rabbits by means of a tube. From 1 to 2 Gm. of cystine per kilogram was introduced in this manner every second or third day. After a few such doses had been taken, the rabbits showed unmistakable signs of kidney injury. It is therefore clear that large amounts of cystine will injure the kidney when it is ingested, as well as when it is injected into the circulation, but the results which are obtained when a large amount of cystine is poured into the fasting stomach cannot be used as a measure of what will follow when an animal slowly eats cystine thoroughly mixed with the other constituents of a diet.

METHOD

In our experiment, white rats were used and were cared for according to the technic of Ferry.[6] All of the animals that were expected to eat the diet containing relatively the smaller amounts of cystine received it by replacement of the cornstarch, either in a standard 18 per cent diet or in an 8 per cent casein diet. The animals that were fed from 2.5 to 20 per cent cystine received it as an addition to the standard 8 per cent casein diet. In addition, each rat daily received 0.05 Gm. of yeast vitamin extract. The cystine used in the experiment was made in this laboratory from hair, by the standard method. The rats can be conveniently dealt with in three groups: *A*, *B* and *C*.

The rats in group *A* all received the basic diet of 18 per cent casein, containing in itself sufficient cystine for growth. Cystine was added to this diet to the extent of 0.5 per cent for two rats, 1.1 per cent for three rats and 2.2 per cent for two rats.

The rats in groups *B* and *C* all received the basic diet of 8 per cent casein. This diet contained too little cystine for growth.

Group *B* consisted of those rats that received from 2.5 to 20 per cent of the diet in the form of cystine for relatively short periods of time. Both adult and young rats were used.

Group *C* consisted of rats, each one of which was taken from its mother at the end of the first month of life, confined in an individual cage and given the appropriate diet. Twenty-five rats were used and separated into six groups: group 1, consisting of five rats, received the basic diet; group 2, consisting of four rats, received the basic diet plus 0.25 per cent cystine; group 3, consisting of four rats, received the basic diet plus 0.75 per cent cystine. Group 4 received the basic diet plus 1 per cent cystine; group 5 received the basic diet plus 1.25 per cent cystine and group 6 received the basic diet plus 1.5 per cent cystine. All except three of the animals were fed according to this plan for approximately one year; one, from the sixth group, lived 284 days, and the other two, from the first and the fifth groups, lived 306 and 283 days, respectively (table 1).

The weight of the rat and the weight of the food eaten were recorded each week. A twenty-four hour specimen of urine from each rat was examined for albumin and casts every second month throughout the period of observation. In addition to this, the urine obtained during the last two series of examinations was subjected to a quantitative, as well as to a qualitative, examination. For

5. Lewis, H. B.: Metabolism of Sulphur; Effect of the Repeated Administration of Small Amounts of Cystine, J. Biol. Chem. **65**:187 (Aug.) 1925.

6. Ferry, Edna L.: J. Lab. & Clin. Med. **5**:735 (Aug.) 1919-1920.

TABLE 1.—*Effect on Growth and on the Kidney of Small But Increasing Amounts of Cystine*

Cystine Added to Diet* %		Initial Weight, Gm.	Maximum Weight, Gm.	Days on Diet: 30 to 90 Albumin	30 to 90 Casts	90 to 150 Albumin	90 to 150 Casts	150 to 210 Albumin	150 to 210 Casts	210 to 270 Albumin	210 to 270 Casts	270 to 330 Albumin, %	270 to 330 Casts, No.	330 to 390 Albumin, %	330 to 390 Casts, No.	390 to 450 Albumin, %	390 to 450 Casts, No.	Outcome
0.00	132	48	144	0	0	0	0	0	0	+	+†	..	..	..	..	..	..	Died of meningitis
	133	56	140	0	0	0	0	0	0	0	0	0	0	..	..	..	..	Died; no tissues saved
	134	56	138	0	0	0	0	0	0	0	0	0	0	..	..	..	..	Died; no tissues saved
	135	54	144	0	0	0	0	0	0	0	0	0	0	..	..	..	..	Died; no tissues saved
	136	58	130	0	0	0	0	0	0	+	0	0	0	0	0	..	..	Kidneys normal
0.25	137	46	202	0	0	+	0	0	0	+	0	0	0	..	..	..	..	Died; no tissues saved
	138	42	180	0	0	+	0	+	0	0	0	0	0	0,1	0	..	..	Kidneys normal
	139	47	186	0	0	+	0	0	0	+	0	0	0	0	0	..	..	Kidneys normal
	140	58	196	0	0	+	0	0	0	+	0	0	0	0	0	..	..	Kidneys congested
0.75	145	49	178	0	0	+	0	+	+	+	+	0	0	0	0	..	..	Edema; cloudy swelling of kidneys; casts
	146	31	190	0	0	+	0	+	+	+	0	0	0	0	0	..	..	Edema of kidneys; many casts
	147	48	210	0	0	+	0	+	+	+	+	0	28	0,3	55	0,2	166	Patchy necrosis; edema; casts
	148	52	200	0	0	+	+	+	+	+	0	0,1	195	0,1	55	..	..	Died; no tissues saved
1.00	149	40	188	0	0	+	+	+	+	+	+	0	153	0,1	199	0,1	96	Patchy edema and necrosis; casts
	150	52	196	0	0	+	+	+	+	+	+	0,1	56	0,1	55	..	..	Patchy necrosis; edema; casts
	151	38	194	0	0	+	+	+	+	+	0	0,1	222	0	55	..	..	Uniform tubular necrosis; casts
	152	47	192	0	0	+	+	0	+	+	+	0	166	0,1	55	..	..	Cloudy swelling and edema of kidneys
1.25	153	46	186	0	0	+	+	+	+	+	+	..	..	..	..	..	..	Died; no tissues saved
	154	38	162	0	0	+	+	+	+	+	+	0	0	0,1	55	..	..	Patchy necrosis and a few casts
	155	52	184	0	0	+	0	0	0	+	+	0	155	0	55	0,1	166	Died; no tissues saved
	156	40	178	0	0	+	0	+	+	+	+	..	..	..	..	..	..	Died; no tissues saved
1.50	141	48	192	+	+	+	+	+	+	+	+	0,4	472	0,1	111	0,1	86	Tubular necrosis; casts; dilated tubules
	142	47	190	+	+	+	+	+	+	..	..	..	..	..	..	..	..	Died; no tissues saved
	143	47	198	+	+	+	+	+	+	+	+	0	220	0	111	..	..	Died; no tissues saved
	144	54	185	+	0	+	+	+	+	0	+	0,1	111	0	111	..	..	Uniform tubular necrosis; patchy edema; casts

* The basic diet contained 8 per cent of protein as casein.

† Died of meningitis day after this examination.

this purpose the amount of albumin contained in a twenty-four hour specimen was measured by the method of Folin,[7] and the total number of casts in the specimen was counted according to the technic of Addis.[8]

When a specimen of urine was to be collected, the rat was placed in a container the general shape of the individual rat cages, the walls of which were made of a sheet of galvanized iron instead of wire mesh. At the bottom of the cage, a horizontal flange projecting inward 1 inch supported a 10-inch funnel. Resting on the funnel was a floor made of galvanized iron wire screening of one-half inch mesh. Immediately below the stem of the funnel, a second, small, funnel, supported by a convenient clamp, contained an egg-shaped bulb which was held away from the sides of this smaller funnel by several glass prongs projecting from the side of the bulb. This smaller funnel drained into a flask containing a crystal of thymol. The rat was confined in this cage by the usual type of weighted screen lid.

Many of the animals in group *B* that received the highest diets died in a few days; the others were killed by a blow on the head. In both cases, the tissues were preserved in formaldehyde for subsequent histologic study.

The animals in group *C* that lived to the end of the experimental period were killed by a blow on the head, and the organs were inspected and preserved in formaldehyde for subsequent study. Tissues were not preserved from the animals that died during the experiment. The weight of both kidneys was obtained within a few minutes after death.

RESULTS OF THE EXPERIMENT

Group A.—These experiments show the effect of the addition of cystine to a diet in itself adequate for growth; that is, one which contains sufficient preformed cystine as measured in terms of growth.

This basic diet has been fed by us to eight rats for eleven months, and to three rats for seventeen months both before and during the time when the cystine diets were being used. All the rats, both control and experimental, have been housed in a single large room under conditions which were identical for all with the exception of the diet. The urine of the control rats that received the diet to which cystine had not been added was examined every other month for the presence of albumin and casts. In addition to this, we have six quantitative determinations of the amount of albumin and the number of casts, if any, after 240 and 450 days of the diet. In not a single instance were any casts found. On the other hand, the tests for albumin were sometimes positive to a slight degree. Other investigators have also noted the irregular occurrence of some substance which is precipitated by heat and acetic acid, and it has been questioned whether this material is albumin in the pathologic sense or whether it is merely an unusually large amount of the precipitable substance normally present in the rat's urine. We have not made any attempt to answer this question, but have considered only heavy albuminurias as evidence of disease. Albuminurias of less than 0.1 per cent do not appear to have a pathologic significance.

7. Folin, J. B. C.: **18**:283, 1914.

8. Addis, Thomas: A Clinical Classification of Bright's Diseases, J. A. M. A. **85**:163-167 (July) 1925.

The addition of as little as 0.5 per cent of cystine to this diet produces evidence of renal injury after the diet has been ingested continuously for four or five months. The three rats that ate the diet containing 1.1 per cent cystine voided urine in which casts were found in small numbers as early as the second month. The number of casts in these urines slowly increased as the feeding continued. The microscopic examination of the kidneys of these animals revealed well marked tubular injury. One of them, rat 129, that was permitted to eat the diet for more than a year, voided grossly hemorrhagic urine at the end of the experimental period, and was killed at this time that we might examine the genito-urinary tract. Sources of hemorrhage other than the kidney were not seen. The two animals whose diet contained 2.2 per cent of cystine both voided abnormal urine within the first month. The kidneys of the animal that died had undergone postmortem changes before preservation. The kidneys of the one that was killed after six months showed the same type of injury in general as that seen in the rats that received half this amount of cystine.

Table 3 makes it clear that the onset of injury is roughly proportional to the concentration of cystine in the diet as indicated by the first appearance of casts. Glomerular injury was not seen in any of the sections.

Group B.—These animals received a basic diet the total protein of which was 8 per cent in the form of casein. Such a diet contains so little preformed cystine when compared to the amount added to the diets fed all these animals that the amount of it in the basic diet may be ignored. The injury may, therefore, be directly compared with the amount of added cystine.

Inspection of table 2 shows that the diet containing 20 per cent of cystine acted as a violent poison. Rat 213 shows how extensive an injury may be obtained within a period of only several days on a diet containing 20 per cent of cystine. The rats that ate the diet containing 10 per cent of cystine also reacted in a way that suggested the effect of a powerful poison, since three out of four were dead in a week. When the diet contained only 5 per cent of cystine the animals were able to survive at least two weeks, at which time they were killed because they were apparently within a few hours of death. A further reduction of cystine to 3.75 per cent of the diet permits continued, but very slow, growth.

The urine column of table 2 shows that within a few hours after the first ingestion highly abnormal urine is obtained from a rat eating the diet highest in cystine content. The 10 per cent cystine diet caused the urinary evidence of injury to appear on the second day. When the diet contains 5 per cent of cystine, it takes approximately twice as long to affect the rat as when 10 per cent of cystine is fed. The urinary

response is delayed a little further when cystine is 3.75 per cent of the diet; and finally, fifteen days elapse before casts appear in the urine when the animal eats the diet containing 2.5 per cent of cystine.

The degree of abnormality seen at autopsy and in the microscopic examination of the kidneys was roughly proportional to the cystine content of the diet.

Figures 1 and 2 show the extent and degree of tubular injury caused by the ingestion for two weeks of a diet containing 5 per cent of

TABLE 2.—*Effect of Large, Increasing Amounts of Cystine on Growth and on the kidney*

Cystine in Diet, Percentage	Rat No.	Initial Weight	Final Weight	Cystine Eaten, Gm. per Kg. per Day	Duration, Days	Urine	Results
20	212	69	62	4.6	2	Much albumin and many casts after 24 hours	Animal died; no tissues saved
	213	85	78	4.1	3	Much albumin and many casts; fat droplets on third day	Widespread tubular necrosis; many casts
10	210	86	68	3.9	7	Much albumin and many casts, second day	Animal died; no tissues saved
	211	84	70	3.1	5	Albumin, casts, red blood cells on fourth day	Animal died; no tissues saved
	221	197	185	1.7	3	Much albumin and many casts on second day	Animal died; no tissues saved
	222	122	115	2.5	3	Albumin, casts, red blood cells on second day	Uniform complete necrosis of tubules; pyknotic nuclei
5	214	65	52	2.6	13	Albumin and casts on fourth day	Figs. 1 and 2
	215	76	50	2.1	14	Much albumin and many casts on fifth day	
3.75	230	124	131	1.6	297	All animals of this group had albumin and casts on the sixth day; these abnormalities persisted to the end	Cloudy swelling of cortex and casts
	231	119	132	1.6	280		
2.5	225	56	92	1.5	280	Albumin and a few casts on the fifteenth day; these observations continued to the end	One large circumscribed area of fibrosis; the remainder showed cloudy swelling

cystine. It should be emphasized that the ingestion of as small an amount as 5 per cent of cystine did produce this widespread necrosis in two weeks.

Group C.—This particular part of the investigation was planned to determine how much cystine, beyond the requirement for growth, could be ingested with impunity. In order to answer this question, it is necessary to know the cystine content of casein. Two different methods have been employed to obtain this information. The older one [9] deter-

9. Van Slyke, D.: J. Biol. Chem. **16**:531, 1913-1914. Jones, D. B.: Gersdorff, C. E. F., and Moeller, O.: The Tryptophane and Cystine Content of Various Proteins, ibid. **62**:183 (Nov.) 1924.

Fig. 1.—A complete section of this kidney is presented to show the pale band located in the lower part of the cortex of the kidney of rat 214 (table 2) which received 5 per cent of cystine in its diet for thirteen days. This band extends around the kidney from pole to pole.

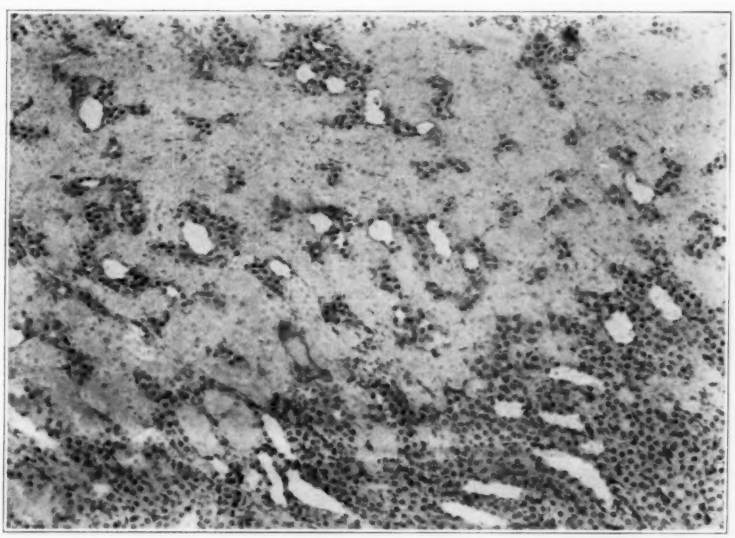

Fig. 2.—Greater magnification of a portion of the necrotic band shown in figure 1. In the lower part of the field fairly normal medullary tubules are seen. The remainder of the field shows almost complete necrosis of the cortex.

mines the cystine by chemical analysis, and the best data indicate that 0.26 per cent of casein can be recovered as cystine. More recently, Sherman [10] determined how much cystine or cystine equivalents are contained in casein, and he concluded that these materials form from 1.3 to 2.5 per cent of it. In what follows we will first calculate the data secured from our feeding experiments, according to the cystine content of casein obtained by chemical analysis, and later recalculate the data, using the results of Sherman's biologic method.

Table 3 presents the total gain in weight for each of the groups in this division. This table shows how poor the growth is on the basic diet; how it is improved by the first addition of cystine; how further improvement is not obtained from larger amounts of cystine; and finally, how further improvement is obtained when the protein of the diet is 18 per cent casein.

Chemical analysis indicates that casein contains 0.26 per cent of cystine. Accordingly, when the protein of the diet is 18 per cent in the form of casein, such a diet will contain 0.47 per cent of cystine. This amount permits good growth. On the other hand, diets containing only 8 per cent of casein with 0.21 per cent of cystine will not permit good growth. Since rats on this type of diet receive a yeast tablet daily, it is necessary to add the cystine content of this material to the calculation.[11] When this is done, it is found that the minimal requirement is approximately 0.06 per cent cystine. The total cystine ingestion on an 8 per cent casein diet is approximately 0.035 per cent.

Table 1 shows that the addition of 0.25 per cent cystine was, as might have been expected, enough to give as good growth as did any further additions; and that this diet, containing approximately five times the minimal cystine requirement, does not cause the animal to ingest enough cystine to injure the kidneys, as determined by urinalysis. When, however, the diet contains 0.75 per cent of cystine, which is approximately thirteen times the requirement, evidence of renal injury in the form of casts begins to appear after five months. The diets containing further small additions of cystine up to and including 1.5 per cent give additional evidence of renal injury, which tends to appear earlier in proportion to the increasing level of cystine.

Our preliminary experiments, however, showed that the addition of 0.5 per cent of cystine to an 18 per cent diet was injurious. The cystine ingested at this level is roughly ten times the minimal requirement. Our data further indicate that the addition of cystine in amounts five times the minimal requirement is harmless, while on the other hand the addition of ten times the required amount of cystine produced evidence of

10. Sherman, H. C., and Woods, Ella: J. Biol. Chem. **66**:29 (Nov.) 1925.
11. McGinty, D. A.; Lewis, H. B., and Marvel, C. S.: J. Biol. Chem. **62**:75 (Nov.) 1924 (M. L. Long's Analysis).

TABLE 3.—*The Relation Between the Amount of Cystine in the Diet and the Kidney Injury*

Rat No.	Sex*	Cystine per Cent Added to Diet†	Initial Weight, Gm.	Days on Diet: 1 to 30		30 to 60		60 to 90		90 to 150		150 to 210		210 to 270		270 to 330		330 to 390		Outcome
				Albumin	Casts	Albumin	Casts	Albumin	Casts	Albumin	Casts	Albumin	Casts	Albumin	Casts	Albumin	Casts	Albumin	Casts	
125	♀	2.2	214	+	+	+	+	+	+	+	+	..	..	..	..	..	..	..	..	Died after 136 days on diet; no tissues saved
126	♀	2.2	38	+	+	+	+	+	+	+	+	+	+	..	..	..	..	..	..	Killed after 181 days on diet; irregular necrosis of tubules; numerous casts
127	♀	1.1	246	0	0	+	0	+	+	+	+	+	+	..	..	..	..	..	..	Killed after 179 days on diet; some tubules are necrotic and take a violet stain typical of calcium; many casts
128	♂	1.1	285	0	0	+	+	..	..	+	+	+	+	..	..	..	..	..	..	Killed after 179 days on diet; tubules of cortex show minor degree of necrosis; many casts
129	♂	1.1	23	0	0	+	+	+	+	+	0	+	+	+	+	+	+	+	+	Killed after 374 days on diet; diffuse hemorrhage in addition to changes described for rat 127
130	♀	0.5	37	0	0	0	0	+	+	+	0	+	0	+	+	+	+	..	..	Died after 270 days on diet; no tissues saved
131	♀	0.5	38	0	0	0	0	+	0	+	+	..	..	..	..	..	..	..	..	Killed after 180 days on diet; minor degree of cloudy swelling and a few casts

* In the table ♀ indicates female, ♂ male.

† The basic diet contained 18 per cent of protein as casein.

injury (table 4). The information at hand does not permit us to determine at what point between these two levels (that is, from five to ten times the requirement) the toxic effects first occur.

Sherman's biologic assay indicates that casein yields not less than 1.3 per cent cystine and not more than 2.5 per cent cystine. In order to simplify the calculations, we will use the average figure of 2 per cent and will not add the cystine content of the vitamin tablet to the total yield of the diet, because the tablet contains a negligible amount of cystine.

By Sherman's method, it is found that the 18 per cent casein diet which gives good growth contains 0.36 per cent of cystine, and that the 8 per cent casein diet on which rats do not grow well yields 0.16 per cent cystine. Our data show that the addition of 0.25 per cent cystine to this 8 per cent diet is harmless. Such rats ingest a diet containing 0.41 per cent cystine. On the other hand, an 18 per cent casein diet to which 0.5 per cent of cystine is added, making a total cystine percentage

TABLE 4.—*Effects of Increasing Amounts of Cystine on Growth and on the General Condition of the Rat*

Chemical Analysis		Biologic Assay		
Amount in Diet, per Cent	Times Requirement	Amount in Diet, per Cent	Times Requirement	Effect
00.035	..	00.160	....	Poor growth
00.080	0	00.360	0	Requirement for growth
00.285	5	00.410	1.1	Harmless
00.560	10	00.860	2.5	Mildly harmful; growth occurs
1.160	17	1.460	4	Moderately harmful; growth occurs
3.880	63	3.910	11	Markedly harmful; growth inhibited
5.000	83	5.000	14	Severely harmful; death in two weeks
10.000	165	10.000	28	Violently harmful; death in five days

of 0.86, is harmful. Hence, on the basis of the biologic assay, it is found that diets containing roughly two and one-half times the requirement are harmful (table 4).

It might be questioned whether the cystine made in the laboratory by hydrolysis gives any information regarding the effect of the preformed cystine as it occurs in the food, since laboratory manipulations might convert a harmless material into a harmful one, even though the hypothetical difference is not yet detectable by the most refined chemical methods. It is easy to show, however, that the cystine we have used is not harmful in the qualitative sense, for the addition of it to a diet containing too little cystine to permit good growth greatly increases the growth promoting quality of the diet.

SUMMARY

1. An 8 per cent casein diet which contains (*a*) 0.021 per cent cystine by chemical analysis, or (*b*) 0.16 per cent cystine by a biologic assay, does not permit good growth.

2. An 18 per cent casein diet which contains (*a*) 0.047 per cent cystine by chemical analysis, or (*b*) 0.36 per cent cystine by a biologic assay, does permit good growth.

3. The addition of 0.25 per cent of cystine to an 8 per cent casein diet is harmless, but the addition of 0.5 per cent cystine to an 18 per cent casein diet is mildly harmful. Accordingly, cystine in the diet becomes harmful when it is 2.5 or ten times the requirement, depending on whether the preformed cystine of the basic diet is determined by biologic assay or by chemical analysis.

The evidence of renal injury increases as the level of the cystine in the diet is raised. Thus, levels ranging around 1.5 per cent of cystine in the diet produce necrosis of the renal tubules in the course of a year. Four per cent of cystine is sufficiently injurious to interfere with the growth of young animals, in addition to producing the injury obtained in lower levels. When 5 per cent of cystine is added to the diet, the effect begins to resemble that of a powerful poison. Animals that are fed such a diet succumb in several weeks. A diet containing 10 per cent of cystine kills in a few days, and when a fifth of the diet is cystine, death follows in two or three days. These large amounts of cystine cause diffuse hemorrhagic necrosis of the renal parenchyma.

THE TOXIC ACTION OF CYSTINE ON THE LIVER OF THE ALBINO RAT*

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While performing the postmortem examination of rats described in a preceding article which deals with the nephrotoxic action of ingested cystine, it was found that liver injury was commonly present in those rats that had ingested the diets containing 0.75 per cent or more of cystine. The livers of those rats that received the largest amounts of cystine were much darker than normal and suggested the color of fresh blood clot; whereas in the rats that had been fed small amounts of cystine, an outstanding gross injury was not detected.

Effect on Rats' Livers of Increasing Amounts of Cystine in Diminishing Intervals of Time

Rat Number	Duration of Feeding, Days	Cystine in Diet, per Cent	Injury
147	409	0.75	Numerous irregular areas of interlobular necrosis
141	409	1.50	Marked degree of constant interlobular necrosis; cells of those areas showed indefinite outlines and pyknotic nuclei; the remainder of the liver tissue showed this same change in a minor degree
251	104	4.00	The tissue showed a generalized fatty infiltration and necrosis most marked about the portal veins
222	4	10.00	Large patches of hemorrhagic necrosis involving especially those areas about the portal veins; remainder of liver tissue showed a marked necrosis
213	4	20.00	Only a small wedge of partially normal cells remained; the remainder of the tissue had been destroyed by hemorrhagic necrosis involving both interlobular and intralobular regions

On microscopic examination it was found that even the addition of 0.75 per cent of cystine to an 8 per cent casein diet gave evidence of well marked injury. Further microscopic study indicated that the degree and extent of the injury was roughly proportional to the amount of cystine in the diet (table 1).

The character of the lesion is described in detail in the accompanying protocols.

EXPERIMENTS ON RATS

RAT 147.—This rat, a female, aged 1 month, was placed on a diet of casein, 8 per cent, to which 0.75 per cent cystine had been added by a replacement of an equal amount of cornstarch in the diet. Its weight was 48 Gm. It remained

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* Aid for this investigation was received from the Ella Sachs Paltz Foundation for the Advancement of Scientific Investigation.

on this diet for twelve months, at which time it was killed. The antemortem weight was 172 Gm.

Necropsy.—The kidneys weighed 1.64 Gm. and were dark, but did not show other gross abnormalities. The surface of the liver showed many small dark areas which suggested hemorrhage. Both the liver and the kidneys were preserved in formaldehyde for histologic study. The other organs did not present any abnormalities.

Microscopic examination of the liver showed numerous patchy interlobular areas of injury. The cells of these regions were necrotic, and had nuclei which were both swollen and pyknotic. These areas stain poorly. Intervening areas of liver tissue were normal (fig. 1).

RAT 141.—This rat, a male, aged 1 month, was placed on a diet of 8 per cent casein, to which 1.5 per cent cystine had been added by replacement, in the diet, of an equal amount of cornstarch. It was killed at the end of one year for examination of its tissues. Its weight at this time was 170 Gm.

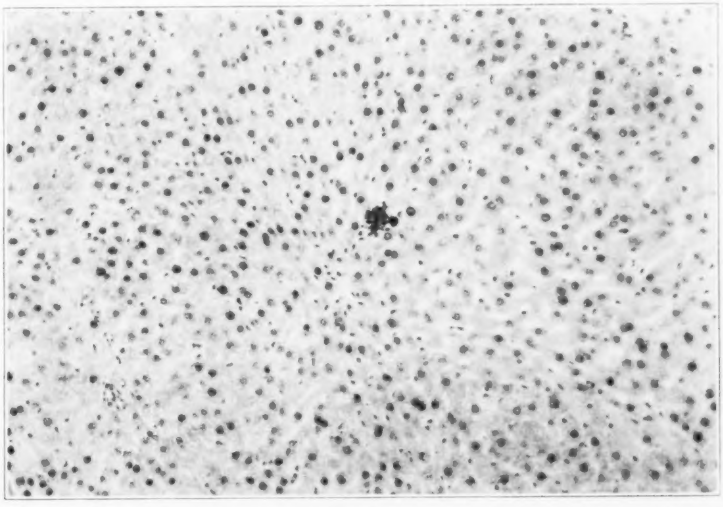

Fig. 1 (rat 147).—Circumscribed areas of moderate injury caused by the ingestion of 2.5 times the minimal requirement of cystine for 409 days.

Necropsy.—The kidneys of this animal were dark chocolate color but did not show other abnormalities. Their weight was 1.56 Gm. The liver was also unusually dark and had numerous small areas in its substance resembling hemorrhage. A piece of the liver and both kidneys were preserved in formaldehyde for subsequent study.

Microscopically, the liver showed a marked constant interlobular necrosis. The cells of these areas were vacuolated, and the small amount of granular cytoplasm remaining took the stain poorly. The poorly stained nuclei were irregular in size, and showed vesicular and pyknotic forms. The remainder of the liver tissue showed this same change in a minor degree (fig. 2).

RAT 251.—A male, weighing 36 Gm., was placed on a diet which contained 15 per cent of protein in the form of dried, powdered, lean beef, to which 4 per cent cystine had been added by replacement of an equal amount of cornstarch. Four weeks later urinalysis showed numerous granular casts and much albumin. These abnormalities persisted until the rat's death. At the end of one hundred and four days the animal was killed. Its weight at this time was 203 Gm.

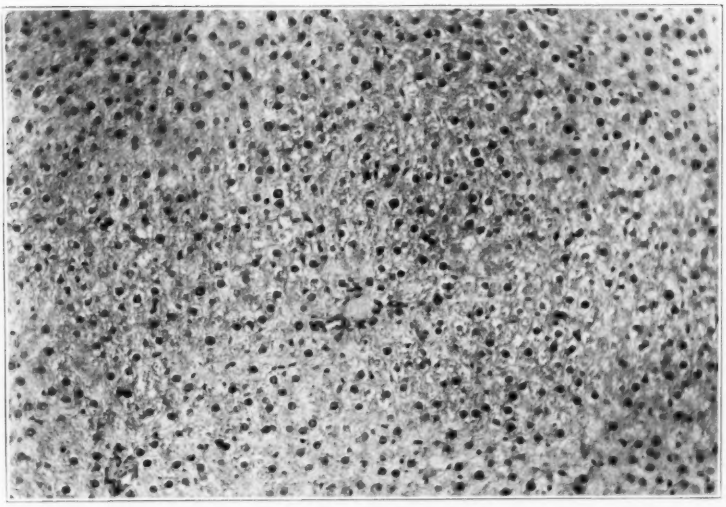

Fig. 2 (rat 141).—Well marked interlobular injury caused by the ingestion of five times the minimal requirement of cystine for 409 days.

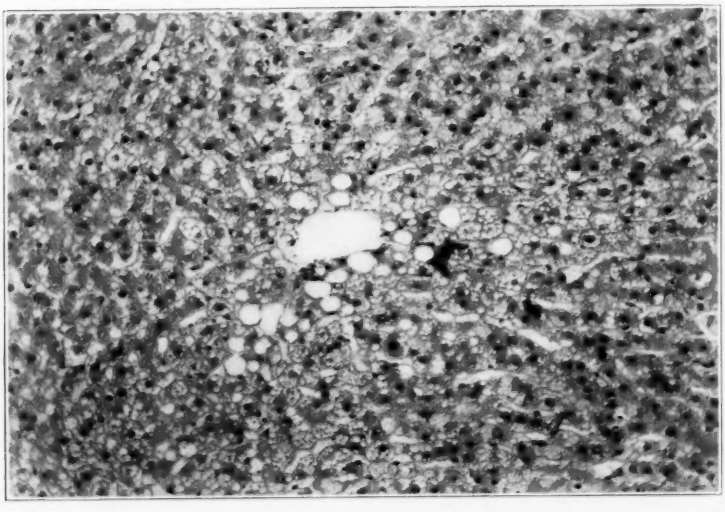

Fig. 3 (rat 251).—Widespread severe cellular injury caused by the ingestion of twelve times the minimal requirement of cystine for 104 days.

Necropsy.—The kidneys of this animal were soft and dark, and showed some subcapsular hemorrhage. The liver was dark and structureless. On section, blood welled from its substance, leaving an irregular surface, caused by the presence of many flat yellow nodules. The urine from the bladder was loaded with granular casts. The other organs and tissues appeared normal.

Microscopically the liver showed a generalized, fatty infiltration and necrosis, most marked about the portal veins. The cell substance was granular and pale. The nuclei were pale in some areas, pyknotic in others and absent in still others. No region had escaped injury. A small amount of cell protoplasm remained, and fat pervaded the whole tissue (fig. 3).

RAT 222.—A male, weighing 122 Gm., was put on a casein, 8 per cent, diet to which 10 per cent cystine had been added, on Dec. 7, 1925. At this time its urine was normal. On Dec. 9, 1926, 5,400 casts were counted in a twenty-four hour specimen of urine. On December 10 the animal was sick. It seemed near death and accordingly was killed. Its weight at this time was 115 Gm.

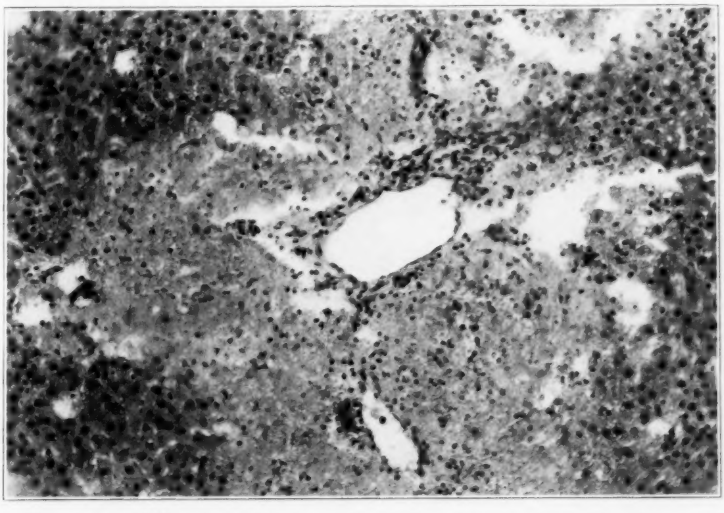

Fig. 4 (rat 222).—Complete necrosis of liver tissue surrounding the portal vein caused by the ingestion of twenty-eight times the minimal requirement of cystine for four days.

Necropsy.—The bladder was distended, and a specimen removed from it by means of a capillary pipet was loaded with red blood cells. The kidneys were mottled with small hemorrhages. The liver presented the same appearance as already described in the protocol of rat 251.

Microscopically the liver showed large patches of hemorrhagic necrosis involving especially the areas about the portal veins. These regions were filled with red blood cells which had entirely replaced the parenchyma. The remainder of the liver showed a severe necrosis with faint cell boundaries and irregular pyknotic nuclei (fig. 4).

RAT 213.—On Nov. 17, 1925, a female, weighing 85 Gm., was put on a casein, 8 per cent, diet to which 20 per cent cystine had been added. Its urine at this time was normal. On Nov. 20, 1925, a specimen of urine was loaded with granular casts and contained albumin. On November 21, the animal appeared sick. Its urine was markedly positive for albumin and had numerous granular casts.

The urine was bright yellow and when stained with scarlet red was positive for fat. The animal weighed 78 Gm. It was killed on this date.

Necropsy.—The kidneys were dark, and subcapsular hemorrhage was evident throughout their surface. On section they were wet and congested. The liver was dark and showed massive hemorrhagic areas which emptied like sinuses when sectioned, leaving an irregular pale yellow surface resembling the livers of rats 251 and 222.

Microscopically, the liver showed a massive hemorrhagic necrosis with only a small wedge of partially normal liver tissue left. In the involved area, cells other than red blood corpuscles were not present. The small wedge of partially normal liver tissue also showed a severe degree of necrosis (fig. 5).

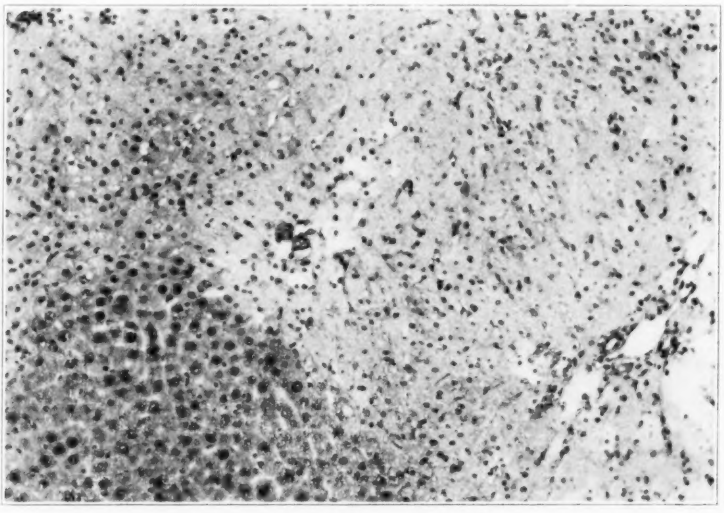

Fig. 5 (rat 213).—Complete interlobular and intralobular necrosis of the liver caused by the ingestion of fifty-six times the minimal requirement of cystine for four days.

SUMMARY

The addition of so little as 0.75 per cent of cystine to an 8 per cent casein diet produces slowly occurring interlobular necrosis of the liver. According to the recently published biologic assay of the cystine content of casein,[1] such a diet contains about 2.5 times the cystine requirement for growth.

Further increases of cystine cause progressively greater injury in diminishing intervals of time.

The presence of 20 per cent of cystine in the diet has caused almost complete necrosis of the liver in four days.

1. Sherman, H. C., and Woods, Ella: Determination of Cystine by Means of Feeding Experiments, J. Biol. Chem. **66**:29 (Nov.) 1925.

WAR GASES AND TUBERCULOSIS

AN EXPERIMENTAL STUDY

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When toxic gases were introduced as a new weapon of warfare, it was the natural reaction of the laity, as well as of the medical profession, to believe that their effects on the lungs would cause a predisposition to pulmonary tuberculosis. This early conclusion, hastily arrived at before there were any facts available for affirming or denying it, has remained largely fixed in the minds of the laity, and also in the minds of a considerable number of physicians. But what are the facts? What have the years during and since the war taught us of the relationship between the war gases and tuberculosis?

Information concerning this question can be gained from two sources: clinical experience, and laboratory experiments. The clinical experiences of many men have been recorded, and include data on thousands of cases of persons who had been gassed. A brief summary of these records will be given below. Except for one or two articles, the experimental side has been largely neglected. It was because of this fact that the present work was undertaken.

HISTORICAL

The early and natural reaction of many physicians of renown was to assume that the effect of war gases on the lungs would be to cause the development of pulmonary tuberculosis, or at least to cause the reactivation of old healed lesions. Sergent and Agnel,[1] Sergent [2] and Mosny [3] expressed the opinion that gassing caused the reactivation of a latent tuberculosis. Sergent and Agnel reported a case of tuberculosis, rapidly progressive and fatal, following gassing with chlorine. However, by 1917 Sergent [4] had changed his mind about the relationship between gassing and tuberculosis and expressed the opinion that tuberculosis was a rare sequel to gassing. In 1925, in discussing the case which he reported with Agnel in 1915, he stated that the patient had

1. Sergent, E., and Agnel, E.: Note sur quelqe effets cliniques des gaz asphyxiants, Bull. et mém. Soc. méd. d. hôp. de Paris **39**:960 (Nov. 5) 1915.
2. Sergent, E.: La tuberculose chez les soldats à la suite des traumatismes du thorax, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1048 (June 30) 1916.
3. Mosney, E.: Le traumatisme et la tuberculose, Bull. et mém.. Soc. méd. d. hôp. de Paris **40**:1062 (June 30) 1916.
4. Sergent, E.: Les suspects de tuberculose, Paris med. (April 7) 1917, quoted by Roubier and Simonin.

been under profound intoxication from the gas, and was left with albuminuria and attacks of recurring purpura.[5] He also added that a short while before the war the soldier had suffered an attack of pulmonary congestion which lasted for three months, and in the course of which there had been several hemoptyses. He thinks that, because of its general nature, the profound intoxication by the gas had the effect of rousing a tuberculosis still active, if not progressive.

Reports before the war of a few isolated cases of pulmonary tuberculosis following prolonged professional exposure to various vapors undoubtedly had its effect on the early formation of opinion following the first gas attacks in 1915. As early as 1886, Poincaré[6] had listed a number of diseases caused by chlorine, and included among them caseous pneumonia. In 1900, Rénon and Latron[7] reported a case of tuberculosis following continuous exposure to chlorine gas in industry. In 1910, Audry[8] reported a case of tuberculosis in a young chemist following prolonged exposure to the vapors of liquor formaldehydi. Sergent refers to the case of Rénon and Latron, and says that its effect on the formulation of opinion was that it tended to double the phthisiogenic rôle of the war gases.

With the exception of the articles mentioned, only a few instances can be found in the literature in which the opinion is expressed that gassing predisposes to tuberculosis.

Boinet[9] stated that the action of gas not only reactivates a latent tuberculosis, but also favors new infection with the tubercle bacillus.

Simonin,[10] in 1920, quoted an unnamed German author who had stated that preexisting tuberculosis may be aggravated by the influence of gas.

In 1918, Dumarest[11] reported a case of tuberculosis following gassing. In 1920, he published another article[12] in which he disagreed with other opinions of the day and cited eleven cases of tuberculosis,

5. Sergent, E.: Les séquelles respiratoires des intoxications par le gaz de combat, Presse méd. **33**:201 (Feb. 14) 1925.

6. Poincaré: Traité d'hygiène industrielle, Paris, 1886, p. 79. Quoted by Rénon and Latron.

7. Rénon, L., and Latron: Intoxication professionelle par les vapeurs de chlore; acué chlorique et tuberculose pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris **17**:436 (April 6) 1900.

8. Audry, quoted by Euthymiou: Etude sur la tuberculose pulmonaire posttraumatique, Thèse de Lyon, 1918.

9. Boinet: Tuberculose pulmonaire consecutive aux traumatismes du thorax et aux gaz asphyxiants, Marseille méd., March, 1919, quoted by Roubier.

10. Simonin, C.: Contribution a l'étude du role étiologique de l'intoxication par les gaz asphyxiants sur le développement de la tuberculose pulmonaire, Thèse de Lyon, 1920.

11. Dumarest: La réforme des tuberculeux, Bull. méd., April 6, 1918. Quoted by Simonin.

12. Dumarest, F.: Tuberculose et gaz asphyxiants, Bull. méd. **34**:374 (April 21) 1920.

either primary or reactivated, following gassing. He also referred to the experimental work of Celli and Guarnieri [13] published in 1886, and quoted them as finding that inoculation with tuberculosis by the air passages was more efficacious after preliminary irritation of these passages. A fuller account of the experiments of these workers will be given below.

In 1921, Sabshin [14] said that he had found 104 cases of chronic pulmonary tuberculosis in 1,200 persons who had been gassed. This would make his percentage of tuberculosis following gassing 8.66 per cent, a much higher figure than has been reported by any one else. He failed to state, however, the history of his patients with regard to tuberculosis before being gassed; the history of gassing is vague, and he did not state on what the diagnosis of tuberculosis was made.

In 1921, Spicer [15] stated that he had "diagnosed a number of cases of tuberculosis two years after the gassing." Details are lacking, however, regarding the basis for the diagnosis.

Hazleton,[16] in 1923, stated that he thinks that coal gas escaping in bedrooms predisposes to tuberculosis. Undoubtedly it does, just as any other factor tending to lower the vitality of the patient might possibly be said to predispose to tuberculosis. He might just as well have said, however, that sleeping in a room with the windows down increases the incidence of tuberculosis.

In addition to the opinions of the foregoing authors, there are a number of isolated instances in which tuberculosis has occurred in persons who have been gassed. In 1916, Ménetrier [17] and Martinez reported the case of a person previously robust who developed phthisis after intoxication by gas. The patient died nine months after gassing. Autopsy showed cavities and tuberculous pneumonia. There were no calcified nodules.

In 1917, Tapie [18] reported the case of a person previously robust, who died from acute tuberculous bronchopneumonia twenty-five days after gassing.

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13. Celli, A., and Guarnieri, E.: Ancora intorno alla profillassi della tubercolosi, Atti. d. r. Accad. med. di Roma **2**:87, 1886.

14. Sabshin, Z. I.: Chronic Effects of War Gassing: Notes on the Examinations of 200 Cases, New York M. J. **114**:232 (Aug. 17) 1921.

15. Spicer, F. W.: The Relation of Chronic Gas Poisoning (Warfare) of the Lungs to Pulmonary Tuberculosis, Minnesota Med. **3**:573 (Dec.) 1920.

16. Hazleton, E. B.: Carbon Monoxide as a Predisposing Cause of Pulmonary Tuberculosis, Brit. M. J. **2**:763 (Oct. 27) 1923.

17. Ménetrier and Martinez: Phthisie pulmonaire consécutive a l'inhalation de gaz asphyxiants, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1083 (July 7) 1916.

18. Tapie, J.: Broncho-pneumonie tuberculeuse aiguë consécutive à une inhalation de gaz asphyxiants, Progrès méd., Oct. 20, 1917. Quoted by Sergent and Roubier.

Gouget,[19] in 1918, reported two cases: One was a reactivation of a latent tuberculosis; the other occurred in a patient without apparent tuberculous antecedents.

Tedeschi,[20] in 1918, reported one case of tuberculosis following gassing, and one case in which an old lesion was reactivated.

Challamel,[21] in 1919, reported a case similar to that of Tapie.

Engel,[22] in 1919, reported a case of acute primary tuberculosis of the larynx caused by gas. Simonin, in commenting on it, expressed the opinion that the case was probably one of reactivation of a preexisting tuberculous laryngitis. He cited the following case of Loeper's [23] to substantiate his views: A soldier died of bronchopneumonia after being overcome by mustard gas. Autopsy showed tuberculous laryngitis, but no tuberculosis of the lungs. There was a history of laryngeal disease for some months before the war.

Simonin,[10] in 1920, reported the following case: After the fatigue and exposure of thirty-one months of active infantry campaigning, a medical officer, recently taken from civil practice, was severely gassed with mustard gas and developed tuberculosis within the next few months.

During the same year, Roubier [24] also reported a case in which he thought that gassing undoubtedly caused the reaction of an old latent tuberculous lesion.

In the isolated observations just cited it does not necessarily follow that because tuberculosis developed after gassing the gassing was the cause of the tuberculosis. It is not a simple question of "post hoc ergo propter hoc." Sergent [5] has recently pointed out that these cases are not necessarily sequelae, but that reactivation of pulmonary tuberculosis occurs conditioned by the profound general effect on the organism; they are not the consequence of a traumatic action occurring locally.

Of the opinions expressed in the literature concerning the relationship between tuberculosis and gassing, the overwhelming majority are to the effect that this relationship is remote. Elliott and Tovell,[25] in

19. Gouget: Gaz irritants et tuberculose, Paris méd., March 2, 1918. Quoted by Sergent.

20. Tedeschi, E.: Gas asfissianti e tubercolosi pulmonare, Riforma med. **34**:2, 1918.

21. Challamel: Blessures du poumon et tuberculose, Paris méd. **9**:186 (March 1) 1919. Quoted by Sergent.

22. Engel, R.: Les séquelles laryngées des gaz, Gaz. d. hôp. Paris **92**:697 (July 26) 1919.

23. Loeper: Sclérose pulmonaire consécutive à l'ypérite, Progrès méd., 1917, no. 10. Quoted by Simonin.

24. Roubier, C.: Intoxication par les gaz et tuberculose pulmonaire, Gaz. d. hôp., Paris **93**:277 (Feb. 21) 1920.

25. Elliott, J. H., and Tovell, H. M.: The Effects of Poisonous Gases as Observed in Returning Soldiers, Internat. J. Surg. **29**:383 (Dec.) 1916.

1916, reported tuberculosis after gassing in three Canadian soldiers with a previous history of tuberculosis, arrested for some years. However, in 1917, Elliott,[26] who had had a large experience with returned soldiers, stated that, "It is very gratifying to be able to state that gas does not seem to have stirred up tuberculosis to any great extent. It was feared that most of the cases would develop into tuberculosis, but very few have." Again in 1919, Elliott [27] stated that among soldiers with tuberculosis in the Canadian army he had found only a few who had become casualties through being gassed.

In 1916, Bernard [28] stated that the facts did not justify the conclusion that tuberculosis was caused by gas.

Gimbert,[29] in 1917, fixed the percentage of cases of tuberculosis apparently caused by the action of gas at 3 per cent. In 1918,[30] in a statistical study made in a center of triage, he found in the previous history of the tuberculous subjects that only a minute proportion of them had been gassed (2.4 per cent).

Moricheau-Beauchamp [31] in 1,206 tuberculous subjects found that only three of them had been gassed.

Léon-Kindberg and Delherm [32] found that of 193 patients with tuberculosis only two had been gassed.

Bernard and Mantoux [33] found that of forty-six patients who had been gassed, only one had tuberculosis, and concluded that the inhalation of gas does not have a noticeable phthisiogenic rôle.

In 1917, Levy and Tronquet [34] stated that it does not seem proved that exposure to gas predisposes to tuberculosis.

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26. Elliott, J. H.: Discussion, Tr. Nat. Tuberc. A., Thirteenth Annual Meeting, 1917, p. 62.

27. Elliott, J. H.: Pulmonary Conditions Simulating Tuberculosis, Am. Rev. Tuberc. **2**:707 (Jan.) 1919.

28. Bernard, L.: Discussion, Bull. et mém. Soc. méd. d. hôp. de Paris **40**: 1074 (June 30) 1916.

29. Gimbert: Action des attaques de gaz sur la tuberculose pulmonaire. Réunion médicale de la Ve Armée, Presse méd., Jan., 1917. Quoted by Sergent, Simonin and Euthymiou.

30. Gimbert: Tuberculose et gaz asphyxiants, Paris méd., Jan., 1918. Quoted by Sergent, Simonin and Euthymiou.

31. Moricheau-Beachamp: Les tuberculoses respiratoires et la guerre, Progrès méd., July 14, 1917. Quoted by Sergent.

32. Léon-Kindberg, M., and Delherm, A.: Sur le triage des tuberculeux aux armées, Presse méd. **25**:645 (Nov. 15) 1917.

33. Bernard, L., and Mantoux, C.: Traumatismes de guerre et tuberculose pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:683 (May 18) 1917.

34. Levy, F., and Tronquet: Un cas d'intoxication par les gaz simulant la tuberculose pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:824 (June 29) 1917.

In 1918, Euthymiou [35] stated that if gases play a rôle in the development of tuberculosis, it seems that chlorine occupies the first rank. However, in 737 cases of tuberculosis, he found only nine patients who had been gassed.

In 1919, Achard [36] found only six cases of tuberculosis in 3,525 persons who had been gassed. He expressed the opinion that the condition was rare following gassing.

In the same year, Rist, Sergent, Dopter and Clerc [37] spoke of the extreme rarity of tuberculosis following gassing.

In studying the condition of 441 persons who had been gassed with mustard gas, and whom they observed for a long period of time, Clerc, Ramond and Guilhaume [38] found only two cases of tuberculosis. One of these patients had shown loss of weight and hemoptysis before being gassed. They believe the condition to be extremely rare following gassing, and state that they have never seen the acute generalized form.

In 1919, Morris [39] stated that in examining old cases of persons who had been gassed, repeated examinations of the sputum failed to reveal tubercle bacilli.

In 1919, Meakins and Priestley [40] followed 700 consecutive cases of gas poisoning through all obtainable records. There was not one case of proved pulmonary tuberculosis in the series.

In 1919, Dennis [41] examined by roentgen ray the chests of a large number of gassed patients but did not find any cases of tuberculosis.

In 1919, Cowen [42] reported a study of "upwards of 150" cases showing the after-effects of gas poisoning, and stated that "the sputum of the great majority of patients was examined, often on several occasions, but in no instance were tubercle bacilli detected."

In 1919, Berghoff [43] served on the Camp Grant Board for the study of the after-effects of war gases on soldiers applying for pensions and gives the following as his conclusion with regard to tuberculosis:

35. Euthymiou, C.: Étude sur la tuberculose pulmonaire post-traumatique, Thèse de Lyon, 1918.

36. Achard, C.: Les séquelles des intoxications par les gaz de combat, Bull. Acad. de méd. **81**:135 (Feb. 4) 1919.

37. Rist, Sergent, Dopter, Clerc: Discussion, Bull. et mém. Soc. d. hôp. de Paris, June 19, 1919. Quoted by Roubier.

38. Clerc, A.; Raymond, L., and Guilhaume, H.: Étude clinique des séquelles pulmonaires chez les ypérités, Presse méd. **27**:477, 1919.

39. Morris, R. S.: Clinical Observations on the Late Pulmonary Effects of Gassing. Contrib. to Med. & Biol. Research, Dedicated to Sir William Osler. **2**:1138, 1919.

40. Meakins, J. C., and Priestley, J. G.: The After-Effects of Chlorine Gas Poisoning, Canad. M. A. J. **9**:968 (Nov.) 1919.

41. Dennis, C. E.: Pulmonary Fibrosis After Gassing, as Shown by X-Rays, M. J. Australia **2**:372 (Nov. 1) 1919.

42. Cowen, S. O.: The After-Effects of Gas-Poisoning, with Special Reference to the Lung Lesions, M. J. Australia **2**:369 (Nov. 1) 1919.

43. Berghoff, R. S.: The More Common Gases: Their Effect on the Respiratory Tract; Observation on Two Thousand Cases, Arch. Int. Med. **24**:678 (Dec.) 1919.

Gas victims, irrespective of the type of gas and severity of attack sustained, show no marked predisposition toward active pulmonary tuberculosis, or toward the reactivation of a healed or quiescent pulmonary lesion.

In 1919, Miller [44] made the following statement:

The infrequent development of pulmonary tuberculosis as the result of exposure to poisonous and irritating gases and of chest wounds raises the question as to whether we have not in the past overemphasized the dangers of mechanical irritation and trauma as exciting causes of active tuberculosis.

In 1920, Mallié [45] stated that cases of tuberculosis referable to gassing were extremely rare.

Benmussa [46] (1920), in analyzing the history of 300 cases of persons who had been gassed, found thirteen cases of pulmonary tuberculosis (4 per cent). These histories were selected from 20,000 histories in Sergent's collection. In discussing Benmussa's results in 1925, Sergent [5] stated that the percentage exceeds those of the statistics of other authors, and that they seem to him the highest figures that one could admit.

Of 162 persons who had been gassed and who showed respiratory sequelae, Rousselot,[47] in 1920, found only one with tuberculosis. He gives gas the lowest place as a factor predisposing to tuberculosis.

In 1920, Sergent and Haas [48] reported analyses of two groups of cases taken from Sergent's 20,000 histories. The first group of 245 histories of cases of persons who had been gassed, all of which showed respiratory sequelae, was chosen without reference to the clinical variety of the sequelae. In these 245 cases, not a single case of pulmonary tuberculosis confirmed by tubercle bacilli in the sputum occurred.

In the second group, they chose 1,600 "suspects" of tuberculosis. In these 1,600 "suspects" they found eighty-five cases of persons who had been gassed. Of these old cases, twenty had tuberculosis. Sergent [5] (1925), in discussing these results, points out that at first glance one is likely to conclude that tuberculosis is frequent in persons who have been gassed; that if one considers how these statistics arise, he is led to recognize that they emanate from a service of "suspects" of tuberculosis and not from a service of simple cases of persons who had been gassed; and that, in consequence, other factors giving rise to tuberculosis must intervene. He further points out that this restric-

44. Miller, J. A.: Tuberculosis Among European Nations at War, Am. Rev. Tuberc. **3**:337 (Aug.) 1919.

45. Mallié, H.: Les séquelles pulmonaires de l'ypérite, J. de méd. de Bordeaux **91**:9 (Jan. 10) 1920.

46. Benmussa, S.: Les séquelles pleuro-pulmonaires et médiastinales des intoxications par les gaz asphyxiants, Thèse de Paris, 1920.

47. Rousselot, H.: Les séquelles pulmonaires chez les intoxiqués par gaz de combat, Thèse de Paris, 1920.

48. Sergent, E., and Haas, J.: La tuberculose pulmonaire et les séquelles des intoxications par les gaz, Médecine **1**:466 (May) 1920.

tion is supported by the fact that the intoxication by the gas in these eighty-five cases was, in the majority of instances, benign and had not always necessitated evacuation.

The conclusions of Sergent and Haas,[48] after their extensive and careful studies, are that tuberculosis following as a direct cause of exposure to gas is exceptional.

In studying 151 cases of persons who had tuberculosis Roubier,[24] in 1920, found that six of these had been gassed. He states, however, that he does not think that the gassing had much to do with the tuberculosis, and mentions the tendency of soldiers to exaggerate and to date all of their troubles from an exposure to gas, even though they got only a whiff of gas under their masks.

Beauchant,[49] as medical consultant in the French army, had the opportunity to see numbers of cases of tuberculosis as well as large numbers of persons who had been gassed. He states that he does not believe that he has seen a single case in which the factor of gas could be looked on indisputably as the cause of tuberculosis, and that among all the persons observed by him who had been gassed with mustard gas and who presented pulmonary sequelae, tuberculosis was not present. Three of 1,206 persons who had tuberculosis had previously been gassed with chlorine.

Among 300 persons who had been gassed, Hunt and Jones [50] found only two who showed signs of phthisis.

In 1920, Simonin [10] published an exhaustive thesis on the relationship between gassing and pulmonary tuberculosis. He states that in fifty-three cases gathered from the literature, mustard was mentioned as the offending gas seven times, and the suffocants eighteen times. He concludes that the mean of all statistics shows that 1 per cent of persons who have been gassed become tuberculous, and that of the cases of tuberculosis in the military population, 2 per cent occur in persons who have been gassed previously. He considered that the latter statement is best established. He further concluded that gas is not so important in the etiology of tuberculosis as are factors of a general nature.

In 1920, Wilson and Mackintosh [51] analyzed a series of 1,500 consecutive mustard gas casualties, and in speaking of Achard's work, they state:

> His view that phthisis is no more than a curiosity as a secondary complication after gassing is in agreement with our experience. We have seen but one example in our series, a case with hemoptysis three days after gassing, in whom at the end of a week tubercle bacilli were found in the sputum. This man had been perfectly fit till he was gassed. Achard points out that there

49. Beauchant, quoted by Simonin (footnote 10).

50. Hunt, G. H., and Jones, quoted by Simonin (footnote 10).

51. Wilson, C. M., and Mackintosh, J. M.: Mustard Gas Poisoning, Quar. J. Med. **13**:201 (Jan.) 1920.

must be many with latent tubercle in the army; yet it is infinitely rare to find the disease light up after gassing. He brings forward experimental support of his conclusion that gas does not create in the lung a soil particularly favorable to the growth of the tubercle bacillus.

Hawes,[52] as regional consultant in diseases of the chest for the New England district of the United States Public Health Service, had a large experience with persons who had been gassed. He states that while gas may lead to the invasion of the bronchi by secondary organisms, yet in his experience tuberculosis plays a minor rôle in this secondary invasion.

Sandall,[53] a medical officer of the British Government, stated in 1922 that there had not been an instance of tuberculosis in the Oxford (England) area in the men pensioned because they had been gassed.

In 1922, Hankins and Klotz [54] selected 166 persons who gave a history of gassing, from 3,837 patients treated at the Johnson City (Tenn.) National Sanatorium. All of these patients had been confined in a hospital for a period of from twenty days to three months because they had been gassed. Sixty-six per cent of the 166 patients had a condition diagnosed as clinical tuberculosis, but the sputum was positive in only one case.

In 1922, Meade [55] summarized the histories of over 3,000 persons examined by the War Risk Insurance Bureau in Kansas City. As a result of his work, he made the following statement: "I now believe that we can say to the public upon the best authority (which is based upon universal observation) that a man is no more liable to tuberculosis as the result of gassing than is a man who has never been gassed."

The following paragraph may also be quoted from Meade:

> I am convinced that all chemical irritants activate and produce certain pathologic changes in the lungs, but I do not believe that such irritants are responsible for tuberculosis and will call your attention to Major Gerald B. Webb's article upon the effects of the inhalation of cigaret smoke in tuberculosis. He concludes that tobacco inhalation is a protective agent against tuberculosis and cites his examination of recruits. There was a much greater number of nonsmokers discharged on account of tuberculosis than were of smokers, and there were fewer cases of tuberculosis among cigaret smokers than among pipe and cigar smokers, showing that the inhalation of the smoke caused an irritation which gave some degree of protection. It has been shown by clinicians for years that coal miners are less susceptible to tuberculosis than are those of ordinary occupations. The Italians observed that sulphur fumes retarded tuberculosis. In London before the trains were electrified the mephitic vapors in the underground tubes were supposed to be of value to the consumptive employees.

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52. Hawes, J. B.: Diagnostic Pitfalls. The Late Effects of Gassing vs. Tuberculosis, Boston M. & S. J. **185**:1 (July 7) 1921.

53. Sandall, T. E.: The Late Effects of Gas Poisoning, Lancet **2**:857 (Oct. 21) 1922.

54. Hankins, J. L., and Klotz, W. C.: Permanent Pulmonary Effects of Gas in Warfare, Am. Rev. Tuberc. **6**:571 (Sept.) 1922.

55. Meade, R. H.: The Late Effect of War Gas on the Lungs and Its Relation to Pulmonary Tuberculosis, J. Missouri M. A. **19**:385 (Sept.) 1922.

Francine later expressed analogous views, as will be seen in the following.

As Consultant in Gas to the American Fourth Army Corps and resident physician-in-chief of the great gas hospital at Toul, France, Francine [56] had an enormous experience with soldiers who had been gassed. In 1922 he made the following statement:

> It is inconceivable that gas (as it is, and not what so many people consider it to be, or what it may have been) could reactivate tuberculosis, and available statistics and majority expert opinion go to prove that it does not do so. This view is endorsed by French, British and other authorities.

Francine's testimony before the senate committee, as reported by Gilchrist [57] in 1924, paints such a vivid picture of his experience with soldiers who had been gassed, and expresses such decided opinions that it is deemed advisable to quote him rather extensively, as follows:

> During the war, of course, I saw very intimately the picture of gas in the field and in the hospital. And this having interested me from the professional point of view, I made a special point of studying the lungs of these gassed men, both clinically and at postmortem in the gas hospital. Clinically the acute picture of gassing, this mass inflammation, disguised the picture at times so that you could not clinically have diagnosed tuberculosis had it been present. But you could examine the sputum. Many of these men spat blood, and their sputum was uniformly negative. . . . .
>
> While we were being rushed, and were too rushed to keep records, I suppose I can say that I saw then 100 to 125 posts. In a number of these cases it was perfectly and palpably evident to a man of pathological training that there were healed, nonactive lesions, which is not an uncommon occurrence, as you know. It is considered that probably 60 to 90 per cent of people have at one time or another had a tuberculosis infection. But these palpable latent lesions showed no evidence of activity, or reactivation, from four to six to ten weeks after the acute inflammation which is supposed to give rise to tuberculosis.
>
> I was only in the hospital six or eight weeks, but there were a number of men unevacuable on account of their condition; they had been severely gassed, and were recuperating, were feeble, were skin and bone, and so on, and they died from an intercurrent infection, which was rampant, as you know, influenza and bronchopneumonia; and they died, not in any sense due, except indirectly, to the gassing, but to this crossinfection. So that those men would have had plenty of time to develop signs of activity in those latent tuberculous lesions. For it takes anywhere from, we will say, two to three weeks for such evidence to appear macroscopically, grossly; for tubercules and localized inflammation to appear, indicating activity; and such would have developed by the time I saw them, if gas had had any effect, any effect whatever, in developing already existing tuberculosis or activity in a latent or healed state.
>
> There was a similar group of cases who were orderlies. We were very short of nurses, and I did not discharge a certain group of men who had been gassed, but whom we had to keep in the hospital to help out as orderlies; these were

56. Francine, A. P.: Tuberculosis and Poison Gas, Tr. Nat. Tuberc. A., Eighteenth Annual Meeting, 1922, pp. 261-264; New York M. J. **117**:25 (Jan. 23) 1923.

57. Gilchrist, H. L.: Warfare Gas and Tuberculosis; Testimony of Dr. Albert P. Francine Before the Senate Committee, Mil. Surgeon **54**:470 (April) 1924.

quite a group. These men had been gassed, but were able to be about and help, carry trays, and so on. Some of these men died through infection, quite a number of them. And these men, again, showing milder pathological evidence of gas, having a history of gas, showed no sign of reactivation in latent lesions. And in the cases I examined postmortem, I should say there were at least twenty to twenty-five men who showed latent or healed lesions—that is, perfectly plain latent lesions—and in not a single case was there any evidence of activity developed through gas. . . . . .

I believe that so far from producing tuberculosis—anybody might, indeed, think so on account of the local irritation in the lungs and bronchi—gas may tend to prevent tuberculosis, and I will tell you why. Because its primary action is to produce congestion of the lungs. In fatal cases it causes severe inflammation followed by congestion and edema and prevents the aeration of the blood, and quickly smothers, so to speak, the patient. He cannot get air into his lungs or blood. When the man drowns or smothers, he is suffering primarily from that inflammation caused not by a germ but a chemical. We know that a nonbacterial congestion or hyperemia is a favorable factor in tuberculosis. In other words, if we could produce locally in the lungs a congestion, we could go far toward curing tuberculosis. People with heart disease (I speak of this simply to you gentlemen as laymen, to explain some of my reasons)—people with heart disease, that type of heart disease known as mitral stenosis, where there is an increase in the blood in the lungs, do not suffer from tuberculosis. . . . .

Further, it has been claimed clinically that men who had tuberculosis and have been gassed run a more favorable, slower, more indolent course, are better off over the same period of time, improve more, than the same type of cases having tuberculosis but who have not been gassed. . . . .

The permanent effect of gas is the result of this irritation, this congestion; and what follows all inflammations and congestions, if they last long enough, is, broadly speaking, the destruction of the finer cellular tissue in places and its replacement by fibroid tissue.

And to that extent these postinfluenzal and postgas lungs show, in the very bad cases, the remains of this thing, and it is still being mistaken for tuberculosis very widely. But they clear up. You take a man that has been gassed and X-ray him when he has recovered from acute symptoms. A plate taken two years later shows, instead of these dark shadows, marked evidence of clearing up. And they do clear up. Their health and strength improve markedly, too. . . . .

It is an interesting thing that, clinically, these gas cases which have tuberculosis do not develop, as a rule, tuberculosis of the throat. You might suppose that where the inflammation had affected the throat originally and very severely, as it may, they would develop as a complication tuberculosis of the throat. They do not. You follow 100 men with tuberculosis who have not been gassed and 100 men with tuberculosis who have been gassed, and the percentage of throat complications, tuberculous laryngitis and of other complications, in the ungassed cases, will, it has been claimed, be greater than in the gassed cases, suggesting, at least, that in some way it inhibits it.

In 1922, Gilchrist [58] compiled an exhaustive report for the Chemical Warfare Service on the relationship between tuberculosis and warfare gases, extracts from which were published in the *Military Surgeon* of the same year. His report quotes many authorities and contains many interesting tables and figures, among which the following are included:

58. Gilchrist, H. L.: Tuberculosis and Its Relation to Warfare Gases, Mil. Surgeon **50**:609 (June) 1922.

Instead of the war increasing the number of tubercular cases, it has lessened them, this being especially true in the different armies, as shown in the following table:

Tuberculosis in Armies

France	Early months of the war	1.75
	Last two years of the war	.63
Great Britain	Before the war, entire army	1.1
	First seventeen months of war, entire army	1.1
Belgium	Before the war, entire army	.35
	During the war, entire army	.26
United States	Regular Army, 1917 to 1918	.75
	National Army, during the war	.67

Gilchrist [59] also quotes the following from the report of the Surgeon General of the Army for 1920:

> One hundred and seventy-three cases of tuberculosis occurred during 1918 and 1919 among the 70,552 men who had been gassed in action. Of this number, 78 had been gassed by gas, kind not specified; 8 by chlorine; 65 by mustard; and 22 by phosgene. The number of cases of tuberculosis for each 1,000 men gassed was 2.45. Since the annual rate of occurrence for tuberculosis among enlisted men serving in Europe in 1918 was 3.50, and in 1919, 4.30 per 1,000, it would seem to be apparent that tuberculosis did not occur any more frequently among the soldiers who had been gassed than among those who had not been.

Furthermore, Gilchrist quotes letters from numerous medical officers who had experience with soldiers who had been gassed during and after the war, and their verdict is almost unanimous to the effect that there is little, if any, relationship between tuberculosis and gassing.

In 1923, Brelet,[60] after studying large numbers of cases of persons who had been gassed, concluded that these men rarely become tuberculous.

McNaught,[61] in discussing the subject in the same year, expresses the same opinion, and says that Meakins and Walker [62] found only one case of tuberculosis in 163 persons suffering from long continued sequelae of being gassed.

Cole,[63] after four years' experience in Veterans' Bureau work, tuberculosis sanatoriums and private practice with soldiers who had been gassed, concludes:

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59. Gilchrist, H. L.: Report on the After Effects of Warfare Gases, Chemical Warfare Service, U. S. A., 1922.

60. Brelet: Note sur les séquelles pulmonaires de l'intoxication par les gaz, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1458 (Nov. 2) 1923.

61. McNaught, P. R.: The Effects, Immediate and Remote, of Irritant Gas (Dichlorethylsulphide) Poisoning on Respiratory Tract, Tubercle **4**:345 (May) 1923.

62. Meakins, J. C., and Walker, T. W.: The After-Effects of Irritant Gas Poisoning, 1918. Quoted by McNaught.

63. Cole, H. H.: A Clinical Study of the Gassed Ex-Soldier with Special Reference to Pulmonary Tuberculosis, Am. Rev. Tuberc. **7**:230 (June) 1923.

War gassing has little to do with the development of later pulmonary tuberculosis. The gassed patient who later develops tuberculosis usually runs a less severe course with less tendency to serious complications than the non-gassed individual.

In 1924, Stewart [64] stated that tubercle bacilli are strikingly absent from the sputum of persons who had been gassed and who show respiratory sequelae. In over 100 cases studied, he found the sputum positive only three times.

In 1924, Spehl [65] stated that the action of gas does not favor the development of pulmonary tuberculosis. Pulmonary tuberculosis, he says, may develop in a patient who has been gassed, but it is difficult to impute it to the direct action of the gas.

Spehl and Dautrebande [66] did not find any instances of tuberculosis in seventy-six persons who had been gassed and who were observed by them. They express the opinion that tuberculosis is a rare sequel of gas, and state that no one has been able to demonstrate convincingly that gas causes the development of tuberculosis or the reactivation of an old lesion.

In his exhaustive article dealing with the late sequelae of gassing, published in 1925, Sergent [5] states that one must conclude from a study of all the statistics that the phthisiogenic rôle of the war gases can be considered almost negligible. He then attempts to interpret the mode of action of the gas when tuberculosis follows intoxication with gas. There are two eventualities: Tuberculosis may immediately follow the intoxication, or it may appear later. In the few isolated instances in which tuberculosis has been reported in the acute or subacute form immediately following gassing, Sergent thinks that the condition arises as the immediate result of two factors, which may be associated with each other or remain isolated: (1) the resowing of the bronchial tree by bacilli coming from lesions, active, but latent, which is favored by the alterations of the mucosa; (2) the profound taint of the organism due to the intoxication, and favored by other conditions (cold, jaded physique and other factors). As to the tuberculosis which occurs late following gassing, Sergent comments that if one takes into consideration, first, the exceptional rarity of cases of tuberculosis following the action of gas, and, second, the great frequency of cases of intoxication by gas, one is led to conclude that the direct action of the gas can be considered negligible, and, further, to believe that indirect factors (diverse miseries

64. Stewart, A.: The Remote Results of "Gassing," M. J. Australia **2**:554 (Nov. 22) 1924.

65. Spehl, P.: Les séquelles des gaz de combat, Arch. méd. belges **77**:1 (Jan.) 1924.

66. Spehl and Dautrebande: Les séquelles des gaz de combat, Arch. méd. belges **77**:768 (Sept.) 1924.

endured during a long campaign, long captivity, poor hygiene, alcoholism, enervating maladies and other conditions), occasionally awaken old tuberculous lesions that have been more or less latent.

Sergent further concludes that whatever may be said of these interpretations, it is incontestable that six years or more after the last possible exposure to gas one encounters some tuberculosis among persons who have been gassed. He is convinced that the longer the time since the end of the war, the more numerous will become the cases of tuberculosis among persons who were gassed during the war. This will signify only that the passage of years will have multiplied the chances for the intervention of the occasional circumstances which favor the reactivation of tuberculosis. It will not be allowable to relate an intoxication by gas which occurred some years before with such a reactivated tuberculous process.

The foregoing is a brief account of all the clinical experience and clinical opinions on the subject that I could find in the literature. It is clear that there is considerable consolidarity of opinion. In order to have the matter definitely settled, it is necessary only to verify clinical opinion by direct experimental evidence. As stated before, there has been little experimental work bearing directly on the subject. The experiments of Achard and Flandin [67] have a direct bearing, but before relating their experiments, I shall briefly review those of several others which bear indirectly on the subject.

In 1886, Celli and Guarnieri [13] conducted a series of experiments on dogs and rabbits to determine whether the inhalation of certain substances would lower the resistance of the animals to subsequent inhalations of dried tuberculous sputum. They first caused seven animals to inhale dried sputum in a special apparatus and found that only one of the seven developed tuberculosis. These were their controls. They then subjected four animals to inhalations of chlorine and subsequently caused them to inhale dried tuberculous sputum. None of the four animals developed tuberculosis. Two animals were then given an intratracheal injection of ammonia followed by inhalations of sputum. These experiments were negative so far as pulmonary tuberculosis was concerned. Scraping of the trachea was done in three animals. One of these animals developed pulmonary tuberculosis as demonstrated by the finding of the bacillus in the lung. In the same manner, four animals were given inhalations of sulphur dioxide. Of these animals, three were infected with pulmonary tuberculosis, while one remained healthy.

While their experiments were negative so far as the chlorine, ammonia and scraping of the trachea were concerned, and positive in the case of the sulphur dioxide, they do not appear to have been of great value, as too few animals were used and as the experiments were not often enough repeated.

67. Achard and Flandin: Note clinique et thérapeutique sur l'intoxication par les gaz, Ministère de la Guerre, 1918.

Corper,[68] in 1919, found that certain local irritants—turpentine, croton oil, tincture of cantharidin and tincture of capsicum—did not have an appreciable effect on the progress of tuberculosis in the guinea-pig, while lamp black had a distinctly retarding influence, and, finally, pulverized glass a markedly accelerating influence when injected with the bacilli. This is in keeping with the known clinical fact that phthisis is not so common among coal miners as among the ordinary population, in spite of the marked amount of anthracosis developed in the lungs from inhaled dust. On the other hand, workers in flint and quartz are especially liable to pulmonary tuberculosis.

The observations of Corper and Rensch,[69] in 1921, on the difference between the reaction of the tubercle bacillus and that of other pathogenic bacteria to leukotoxic agents are interesting and worth while quoting:

> It is interesting in this connection that tuberculosis in the animal is not perceptibly influenced by agents and procedures having a profound effect on acute experimental infections. Corper and Chovey found that mice subjected to a single nonlethal exposure to the roentgen ray, capable however of producing a leukopenia, or given a nonfatal injection of thorium X, also capable of causing leukopenia, and shortly thereafter inoculated with pneumococci or hemolytic streptococci, human and bovine, revealed an increased susceptibility to all of these organisms, as indicated by an increased and earlier mortality among the treated animals and the earlier appearance in, and longer persistence of, the cocci in the blood, as compared with animals subjected only to inoculation. Winternitz and his co-workers found that benzene had a similar effect on pneumococcus infection in rabbits, while Läwen found that prolonged roentgen-ray exposure of rabbits increased their susceptibility to staphylococcus infections, and that the resistance of mice to pyocyaneus and anthrax, and rats to anthrax was reduced by roentgenization. The tubercle bacillus, however, stands out distinctly from these organisms in respect to the leukotoxic agents as noted by Corper, Kellert, and Weinberg, the course of tuberculosis in guinea-pigs being uninfluenced by benzene, thorium X and the roentgen ray.

These authors also conducted a series of experiments to determine the action of mustard gas on the development of tuberculosis in guinea-pigs. They first found that mustard gas dissolved in 25 per cent glycerol is bactericidal toward virulent human tubercle bacilli after an exposure in vitro of at least one-half hour to 0.1 per cent, and after two hours to 0.01 per cent. They then found that mustard gas in 0.1 per cent strength in 25 per cent glycerol, containing virulent human tubercle bacilli, and injected immediately subcutaneously into guinea-pigs, entirely prevented the development of systemic tuberculosis; even 0.01 per cent mustard gas had a distinctly retarding influence on the development of

68. Corper, H. J.: Further Attempts to Reduce the Resistance of the Guinea-Pig to Tuberculosis; The Effects of Various Local Irritants, Am. Rev. Tuberc. **3**:605 (Dec.) 1919.

69. Corper, H. J., and Rensch, O. B.: The Effect of Mustard Gas (Dichlorethyl sulphide) on Experimental Tuberculosis, J. Infect. Dis. **28**:286 (March) 1921.

tuberculosis in these animals. They also found that mustard gas given subcutaneously to guinea-pigs in amounts consistent with life (0.0001 cc. in glycerol) in a single injection, or repeated at four day intervals for three or four injections, did not have an appreciable effect on the amount of anatomic tuberculosis resulting from the subcutaneous injections of virulent human tubercle bacilli.

In 1922, Conroy, Conroy and Laird [70] found that chlorine (6 parts per million) effectively rid the sewage from a sanatorium for tuberculosis of tubercle bacilli. Of twenty-four guinea-pigs inoculated with this effluent untreated with chlorine, twenty-one developed tuberculosis. None of the thirty inoculated with effluent after treatment with chlorine became tuberculous.

In 1918, Achard and Flandin [67] conducted a series of experiments to determine the direct effect of the inhalation of gas on the development of pulmonary tuberculosis. They submitted guinea-pigs to the repeated intoxications of carbon monoxide, and concluded that tuberculosis did not progress more rapidly and that it was not more severe in these animals than in control guinea-pigs inoculated the same day with the same dose of bacilli.

EXPERIMENTAL

While these last mentioned experiments are extremely interesting and of great value for their direct bearing on the relationship between gassing and the development of pulmonary tuberculosis, it seemed advisable to conduct further experiments, employing gases used in actual warfare, in the hope of more definitely settling the question of the relationship between tuberculosis in the ex-soldier and a history of gassing during the late war. To this end I have conducted experiments covering the past three and one-half years, in the course of which 335 rabbits were used. The gases used were mustard, phosgene and lewisite.

METHOD

The method employed in each set of experiments has been to use an equal number of controls and of animals inoculated with tubercle bacilli. The controls and inoculated animals have received the same amount of gas, both as to the time and concentration, in each instance. In order to simulate time relations between gassing and a possible infection with tubercle bacilli that might occur in actual warfare, I have inoculated different groups of animals at varying times before gassing, and other groups at varying times after gassing. In the former instances we hoped to simulate an old latent tuberculous lesion, and to

70. Conroy, J. M.; Conroy, B. B., and Laird, A. T.: The Destruction of Tubercle Bacilli in Sewage by Chlorine, Am. Rev. Tuberc. **6**:63 (March) 1922.

determine whether gassing would have any effect on reactivating or accelerating the process. In the latter we attempted to determine the effect of gassing on the beginning of a new tuberculous infection.

Rabbits were used in all the experiments, as it is easier to produce pulmonary tuberculosis in them than in the other laboratory animals. All injections were made intravenously in the ear vein. This resulted in an active pulmonary tuberculosis, the extent of which could be controlled to a large degree by the size of the dose injected. The liver, kidneys and spleen were the other organs affected, but these were never affected to the same extent as the lungs. It was possible to produce a pulmonary tuberculosis without the involvement of other organs if the dose was kept small enough. Intratracheal injection was tried, but was not nearly so satisfactory as injection into the ear vein.

Glycerine broth cultures of virulent human tubercle bacilli were used in all the experiments. Young cultures were used in all instances. Varying doses were given, in milligrams per kilogram of body weight. In order to secure uniformity of weighing conditions, the fluid was poured off, and the culture was always allowed to drain for one-half hour before it was weighed. In the early experiments the large dose used produced tuberculosis in practically all animals inoculated. Later an effort was made to give doses so small that part of the animals that received injections would contract the disease and part would not. In this way, the effect of the gas as a phthisiogenic agent could be more easily determined.

In order to allow sufficient time for the development of tuberculous lesions, should there be any, animals were not killed in less than five weeks from the time of inoculation. This allowed plenty of time for the development of the lesion. Indeed, many animals died of tuberculosis in a much shorter period of time from the date of inoculation—several in three weeks, and one or two in two weeks.

An account was kept of the gain or loss in weight of all animals, but it proved valueless, and is not mentioned further in this paper. Rabbits are capricious in the matter of weight; some with well developed tuberculous lesions gain steadily, while others without tuberculosis or other demonstrable lesions lose weight with surprising rapidity.

All the animals gassed were gassed with as near the lethal dose of the gas employed as it was possible to give them without causing death. Even with this sublethal (i. e., below average lethal) dose some of the animals died from the effects of the gas. These large doses were used because we wanted to repeat as nearly as possible the conditions that prevailed for the soldiers that were the most severely gassed during the war.

Mustard and phosgene were selected as the principal gases for the experiments because they produce two distinct types of pulmonary lesions. Mustard produces an extensive necrotizing inflammatory reac-

tion involving the entire respiratory tract, including the lung parenchyma; phosgene produces an intense edema, so intense that in severe cases the patient actually drowns in his own body fluids. All the other war gases produce lesions which are gradations and combinations of these two extremes. Intercurrent infections, of course, are common to them all.

Examples of representative experiments are shown in the tables. In choosing the sets of experiments for these tables, an effort was made to make a variety of selections both as to the gas used and as to the length of time before and after the inoculation that the animals were gassed. The details of a rather large number of experiments are given

TABLE 1.—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	PHOSGENE						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			Controls				
45	5	5/15/24	Killed	36 days	.....	++++	Liver, spleen
46	5	5/15/24	Died	6 days	.....	.....	
47	5	5/15/24	Died	9 days	.....	.....	
48	5	5/15/24	Killed	36 days	.....	++++	Liver, spleen, kidneys
49	5	5/15/24	Killed	36 days	.....	++++	Liver
			Gassed	Animals			
50	5	5/15/24	Killed	36 days	20 hours after	++++	Liver, spleen
51	5	5/15/25	Killed	35 days	20 hours after	++++	
52	5	5/15/24	Died	21 days	20 hours after	++++	
53	5	5/15/24	Killed	36 days	20 hours after	++++	Liver, spleen
54	5	5/15/24	Died	4 days	20 hours after	.....	

Eighteen day old glycerine broth culture used for inoculations.
The last five animals in the table were gassed with phosgene (concentration 0.29 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty hours after inoculation.
The plus marks indicate the number of lobes involved.

in these tables. This is considered necessary for clarity. The results in the experiments not included in the tables were similar to the results in those included.

A casual glance at the tables clearly shows the verdict. Only a discriminating person would be able to say whether there was more or less tuberculosis in the animals that were gassed than in those that were not gassed. The amount of tuberculosis was uniformly the same in the controls and in the gassed animals throughout the experiments. This is true both as to the extent of the tuberculous lesions (number of lobes involved) and as to the severity of the lesions. The lungs, liver, spleen and kidneys of all animals were examined carefully, both grossly and microscopically, and the results given in the tables represent the sum total of the tuberculosis found by both methods of examination.

An exception to the conclusions of the preceding paragraph might be considered with respect to the cases in which lewisite was used, namely, if it could be said that any difference existed, there was less tuberculosis in the gassed animals than in the controls. This is clearly shown in

TABLE 2.—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			PHOSGENE				
			Controls				
63	2.5	6/25/24	Killed	36 days	.....	++++	
64	2.5	6/25/24	Killed	36 days	.....	+	
65	2.5	6/25/24	Killed	36 days	.....	++	
66	2.5	6/25/24	Killed	36 days	.....	++++	
67	2.5	6/25/24	Killed	36 days	.....	++	
			Gassed	Animals			
68	2.5	6/25/24	Died	14 days	20 hours after	.....	
69	2.5	6/25/24	Killed	36 days	20 hours after	.....	
70	2.5	6/25/24	Died	2 days	20 hours after	.....	
71	2.5	6/25/24	Died	5 days	20 hours after	.....	
72	2.5	6/25/24	Killed	36 days	20 hours after	++++	

Nine day old glycerine broth culture used for inoculations.
The last five animals in the table were gassed with phosgene (concentration 0.54 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty hours after inoculation.
The plus marks indicate the number of lobes involved.

TABLE 3.—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			PHOSGENE				
			Controls				
78	2.5	7/14/24	Died	27 days	.....	++++	Liver
79	2.5	7/14/24	Killed	46 days	.....	+++	Spleen
80	2.5	7/14/24	Killed	46 days	.....	++++	Liver, kidneys
81	2.5	7/14/24	Killed	46 days	.....	++++	Liver
82	2.5	7/14/24	Killed	46 days	.....	++++	Liver
			Gassed	Animals			
73	2.5	7/14/24	Killed	46 days	20 hours after	++++	
74	2.5	7/14/24	Died	8 days	20 hours after	.....	
75	2.5	7/14/24	Killed	46 days	20 hours after	++++	
76	2.5	7/14/24	Died	9 days	20 hours after	.....	
77	2.5	7/14/24	Died	3 days	20 hours after	.....	

Culture used was incubated for twenty-two days, then placed in the icebox for three days, and again incubated for three days before injection.
The last five animals in the table were gassed with phosgene (concentration 0.49 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty hours after inoculation.
The plus marks indicate the number of lobes involved.

tables 12 to 15. One of the experiments with phosgene (table 2) also shows less tuberculosis in the gassed animals than in the controls. This is in keeping with Francine's statement (given in this article) that gassing lessens the chances for the development of pulmonary tuberculosis, owing to the state of congestion produced in the lungs.

It is possible that other experiments with phosgene and mustard would have shown the same thing if smaller doses had been used for the inoculations. For convenience, in the tables the number of lobes involved has been used as the index of infection. In most of the phosgene and mustard experiments such large doses were used that all lobes, both of

TABLE 4.—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	PHOSGENE						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			Controls				
194	.5	3/7/25	Killed	77 days	.....	++++	Kidney
195	.5	3/7/25	Died	72 days	.....	++++	
196	.5	3/7/25	Died	25 days	.....	++++	
197	.5	3/7/25	Killed	77 days	.....	++++	
198	.5	3/7/25	Killed	77 days	.....	++++	Kidney
199	.5	3/7/25	Died	34 days	.....	++++	
200	.5	3/7/25	Killed	77 days	.....	++++	Kidney
			Gassed	Animals			
201	.5	3/7/25	Killed	77 days	37 days after	++++	
202	.5	3/7/25	Killed	77 days	37 days after	++++	
203	.5	3/7/25	Died	43 days	37 days after	++++	
204	.5	3/7/25	Killed	77 days	37 days after	++++	
205	.5	3/7/25	Died	51 days	37 days after	++++	

Nine day old glycerine broth culture used for inoculations.
The last five animals in the table were gassed with phosgene (concentration 0.54 mg. of phosgene in 1 liter of air for seven and one-half minutes) thirty-seven days after inoculation.
The plus marks indicate the number of lobes involved.

TABLE 5.—*Results Showing the Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	PHOSGENE						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			Controls				
214	.1	5/2/25	Died	3 days	.....	.....	
215	.1	5/2/25	Killed	41 days	.....	++++	Liver
			Gassed	Animals			
216	.1	5/2/25	Killed	41 days	21 days before	++++	
217	.1	5/2/25	Killed	41 days	21 days before	++++	

Eight day old glycerine broth culture used for inoculations.
The last two animals in the table were gassed with phosgene (concentration 0.51 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty-one days before inoculation.
The plus marks indicate the number of lobes involved.

the animals that were gassed and of those that were not, became infected. In most instances, however, the infection was not severe in any lobe, and on both gross and microscopic examinations a difference in the amount of tuberculosis in the gassed animals and in the controls could not be detected.

TABLE 6.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			MUSTARD				
			Controls				
85	2.5	7/21/24	Killed	46 days	.....	++++	
86	2.5	7/21/24	Killed	46 days	.....	++++	Liver, spleen
87	2.5	7/21/24	Killed	46 days	.....	++++	
88	2.5	7/21/24	Died	6 days	.....	++++	
89	2.5	7/21/24	Killed	46 days	.....	++++	
			Gassed Animals				
90	2.5	2/21/24	Killed	46 days	20 hours after	++++	
91	2.5	7/21/24	Died	27 days	20 hours after	++++	Liver
92	2.5	7/21/24	Killed	46 days	20 hours after	++++	
93	2.5	7/21/24	Killed	46 days	20 hours after	++++	
94	2.5	7/21/24	Killed	46 days	20 hours after	++++	
95*	2.5	7/21/24	Killed	46 days	26 days before	++++	

Thirteen day old glycerine broth culture used for inoculations.

* Rabbits numbers 90 to 94, inclusive, were gassed with mustard (concentration 0.0114 mg. of mustard in 1 liter of air for one hour) twenty hours after inoculation. Rabbit no. 95 had been gassed with phosgene (concentration 0.54 mg. of phosgene in 1 liter of air for seven and one-half minutes) twenty-six days previous to inoculation.

The plus marks indicate the number of lobes involved.

TABLE 7.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			MUSTARD				
			Controls				
116	1	9/27/24	Killed	39 days	.....	++++	Liver
117	1	9/27/24	Killed	39 days	.....	++++	Kidney, spleen
118	1	9/27/24	Killed	39 days	.....	++++	Kidney
119	1	9/27/24	Killed	39 days	.....	++++	Liver
120	1	9/27/24	Killed	39 days	.....	++++	
121	1	9/27/24	Killed	39 days	.....	++++	
			Gassed Animals				
110	1	9/27/24	Killed	39 days	48 hours after	++++	
111	1	9/27/24	Killed	39 days	48 hours after	++++	Liver, spleen
112	1	9/27/24	Killed	39 days	48 hours after	++++	Liver, kidney
113	1	9/27/24	Killed	39 days	48 hours after	++++	Liver, spleen kidney
114	1	9/27/24	Killed	39 days	48 hours after	++++	
115	1	9/27/24	Killed	39 days	48 hours after	++++	

A two to three weeks old glycerine broth culture used for inoculations.

The last five animals in the table were gassed with mustard (concentration 0.0148 mg. of mustard in 1 liter of air for one hour) forty-eight hours after inoculation.

The plus marks indicate the number of lobes involved.

TABLE 8.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	MUSTARD						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			Controls				
188	.5	2/28/25	Killed	73 days	.....	++++	
189	.5	2/28/25	Killed	73 days	.....	++++	
190	.5	2/28/25	Killed	73 days	.....	++++	
191	.5	2/28/25	Killed	73 days	.....	++++	
192	.5	2/28/25	Killed	73 days	.....	++++	
193	.5	2/28/25	Killed	73 days	.....	++++	
			Gassed	Animals			
182	.5	2/28/25	Died	36 days	5 weeks after	++++	
183	.5	2/28/25	Died	42 days	5 weeks after	++++	
184	.5	2/28/25	Died	61 days	5 weeks after	++++	
185	.5	2/28/25	Killed	73 days	5 weeks after	++++	
186	.5	2/28/25	Killed	73 days	5 weeks after	++++	
187	.5	2/28/25	Killed	73 days	5 weeks after	++++	Liver, spleen

Seven day old glycerine broth culture used for inoculations.

The last six animals in the table were gassed with mustard (concentration 0.0138 mg. of mustard in 1 liter of air for one hour) five weeks after inoculation.

The plus marks indicate the number of lobes involved.

TABLE 9.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	MUSTARD						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			Controls				
122	1	10/4/24	Died	21 days	.....	++++	Liver, spleen
123	1	10/4/24	Killed	34 days	.....	++++	Liver, spleen, kidney
124	1	10/4/24	Died	16 days	.....	++++	
125	1	10/4/24	Killed	34 days	.....	++++	
126	1	10/4/24	Killed	34 days	.....	++++	Liver, spleen, kidney
127	1	10/4/24	Killed	34 days	.....	++++	
			Gassed	Animals			
128	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
129	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
130	1	10/4/24	Killed	34 days	28 hours before	++++	Kidney
131	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, kidney
132	1	10/4/24	Killed	34 days	28 hours before	++++	Liver, spleen, kidney
133	1	10/4/24	Died	18 days	28 hours before	++++	Liver,

Fourteen day old glycerine broth culture used for inoculations.

The last six animals in the table were gassed with mustard (concentration 0.0145 mg. of mustard in 1 liter of air for one hour) twenty-eight hours previous to inoculation.

The plus marks indicate the number of lobes involved.

TABLE 10.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			MUSTARD				
			Controls				
152	.5	12/13/24	Killed	42 days	.....	++++	Liver, spleen
153	.5	12/13/24	Killed	42 days	.....	++++	Spleen
154	.5	12/13/24	Killed	42 days	.....	++++	Liver
155	.5	12/13/24	Killed	42 days	.....	++++	Liver
156	.5	12/13/24	Killed	42 days	.....	++++	Spleen
157	.5	12/13/24	Killed	42 days	.....	++++	
			Gassed	Animals			
146	.5	12/13/24	Killed	42 days	31 days before	++++	Liver, spleen
147	.5	12/13/24	Killed	42 days	31 days before	++++	
148	.5	12/13/24	Killed	42 days	31 days before	++++	Spleen
149	.5+	12/13/24	Killed	42 days	31 days before	++++	Liver
150	.5	12/13/14	Killed	42 days	31 days before	++++	Liver, kidney
151	.5	12/13/24	Killed	42 days	31 days before	++++	Liver, spleen

Fifteen day old glycerine broth culture used for inoculations.

The last six animals in the tables were gassed with mustard (concentration 0.016 mg. of mustard in 1 liter of air for one hour) thirty-one days previous to inoculation. At the same time six other rabbits, not used in the experiment, were gassed with the same concentration, but died from the effects of the gas. This is mentioned only to indicate that the concentrations used were as near the lethal point as could be attained without killing all the animals.

The plus marks indicate the number of lobes involved.

TABLE 11.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			MUSTARD				
			Controls				
274	.01	9/14/25	Killed	8 months	.....	++++	
275	.01	9/14/25	Killed	8 months	.....	++	Kidneys
276	.01	9/14/25	Killed	8 months	.....	++	
277	.01	9/14/25	Killed	43 days	.....	++++	
278	.01	9/14/25	Killed	43 days	.....	+++	
279	.01	9/14/25	Killed	43 days	.....	++++	
			Gassed	Animals			
268	.01	9/14/25	Killed	43 days	1 day after	++++	
269	.01	9/14/25	Killed	43 days	1 day after	++++	
270	.01	9/14/25	Died	10 days	1 day after	.....	
271	.01	9/14/25	Killed	8 months	1 day after	+	
272	.01	9/14/25	Killed	8 months	1 day after	++	
273	.01	9/14/25	Killed	8 months	1 day after	++	

Ten day old glycerine broth culture used for inoculations.

The last six animals in the table were gassed with mustard (concentration 0.0114 mg. of mustard in 1 liter of air for one hour) twenty-four hours after inoculation.

The plus marks indicate the number of lobes involved.

Animals inoculated with tubercle bacilli some weeks before gassing showed about the same amount of tuberculosis when they were killed several weeks after gassing as control animals that were inoculated at the same time with the same dose of bacilli. This tends to bear out the clinical observations that gassing does not reactivate an old tuberculous lesion.

Likewise, animals gassed at varying periods of time before inoculation with tubercle bacilli developed no more tuberculosis than did control

TABLE 12.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	LEWISITE						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
				Controls			
280	0.01	9/26/25	Killed	70 days	.....	++++	
281	0.01	9/26/25	Killed	70 days	.....	++	
282	0.01	9/26/25	Killed	70 days	.....	++++	
283	0.01	9/26/25	Killed	70 days	.....	+++	
284	0.01	9/26/25	Killed	70 days	.....	++++	
				Gassed Animals			
285	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	++++	
286	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	+	
287	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	+++	
288	0.01	9/26/25	Died	4 days	8 days before	.....	
289	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	+++	
290	0.01	9/26/25	Died	26 days	8 days before and 6 days after	.....	
291	0.01	9/26/25	Killed	70 days	8 days before and 6 days after	++	

Four day old glycerine broth culture used for inoculations.

The last six animals were gassed with the lewisite in a field test eight days before inoculation, and were gassed with the same gas in a gassing chamber (concentration 0.0069 mg. of lewisite in 1 liter of air for one hour) six days after intoculation.

The plus marks indicate the number of lobes involved.

animals inoculated at the same time with the same dose of bacilli. This again supports the view of those clinicians who believe that gassing does not have any influence on the development of new tuberculous lesions.

The results with animals gassed almost immediately (less than twenty-four hours) before or after inoculation with tubercle bacilli were the same as with those gassed for longer periods of time before or after inoculation.

TABLE 13.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			LEWISITE				
			Controls				
292	0.01	10/3/25	Died	22 days	.....	++++	Spleen
293	0.01	10/3/25	Killed	67 days	.....	++++	
294	0.01	10/3/25	Killed	67 days	.....	++++	
295	0.01	10/3/25	Killed	67 days	.....	++++	
296	0.01	10/3/25	Killed	67 days	.....	++++	
			Gassed	Animals			
297	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	++	
298	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	+	Kidney
299	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	+++	
300	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	++++	
301	0.01	10/3/25	Killed	67 days	15 days before and 2 days after	+++	

Eleven day old glycerine broth culture used for inoculations.

All rabbits were gassed with lewisite in a field test fifteen days before inoculation. The last five animals in the table were also given the same gas in a gassing chamber (concentration 0.0073 mg. of lewisite in 1 liter of air for one hour) two days after inoculation.

The plus marks indicate the number of lobes involved.

TABLE 14.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			LEWISITE				
			Controls				
318	.005	12/19/25	Died	4 days	.....	.....	
319	.005	12/19/25	Died	28 days	.....	.....	
320	.005	12/19/25	Killed	42 days	.....	++++	
321	.005	12/19/25	Missing	.....	.....	Missing	
322	.005	12/19/25	Killed	42 days	.....	+++	
323	.005	12/19/25	Killed	42 days	.....	++++	
			Gassed	Animals			
312	.005	12/19/25	Killed	42 days	5 days after	+	Kidney spleen
313	.005	12/19/25	Killed	42 days	5 days after	+++	
314	.005	12/19/25	Killed	42 days	5 days after	.....	
315	.005	12/19/25	Killed	42 days	5 days after	++	
316	.005	12/19/25	Killed	42 days	5 days after	++	
317	.005	12/19/25	Killed	42 days	5 days after	+++	

Nine day old glycerine broth culture used for inoculations. The culture was not growing especially well.

The last six animals were gassed with lewisite (concentration 0.0067 mg. of lewisite in 1 liter of air for one hour) five days after inoculation.

The plus marks indicate the number of lobes involved.

The experiment tabulated in table 11 is interesting in that half of the gassed animals and half of the controls were kept for a much longer period of time than usual—eight months—before they were killed. The other half of both controls and gassed animals were killed at the end of six weeks, and all showed well developed tubercles in all lobes. It is reasonable to assume that at the time the first half were killed (six weeks after inoculation) the other half had about the same amount of tuberculosis. Keeping this latter half for a long period of time should then show the ultimate tendency of the existing tuberculosis. When these

TABLE 15.—*Results Showing Extent of Tuberculosis in Animals That Were Gassed and in Those That Were Not Gassed*

	LEWISITE						
No.	Dose in Milligrams per Kilogram of Body Weight	Date Injected	Result	Time Between Injection and Autopsy	Time of Gassing in Relation to Injection	Lung Involvement	Other Organs Involved
			Controls				
330	.005	2/6/26	Killed	42 days	.....	+	
331	.005	2/6/26	Killed	42 days	.....	+	
332	.005	2/6/26	Killed	42 days	.....	++++	
333	.005	2/6/26	Killed	42 days	.....	.....	
334	.005	2/6/26	Killed	42 days	.....	.....	
335	.005	2/6/26	Died	14 days	.....	.....	
			Gassed Animals				
324	.005	2/6/26	Killed	42 days	1 day before	++++	
325	.005	2/6/26	Killed	42 days	1 day before	+	
326	.005	2/6/26	Killed	42 days	1 day before	+	Spleen
327	.005	2/6/26	Killed	42 days	1 day before	.....	
328	.005	2/6/26	Killed	42 days	1 day before	+	
329	.005	2/6/26	Killed	42 days	1 day before	.....	

Ten day old glycerine broth culture, growing luxuriously, used for inoculations.
The last six animals were gassed with lewisite (concentration 0.00233 mg. of lewisite in 1 liter of air for one hour) twenty-four hours previous to inoculation.
The plus marks indicate the number of lobes involved.

TABLE 16.—*Incidence of Lesions in Spleen, Liver and Kidneys*

	Total Number	Spleen	Liver	Kidneys
Gassed animals	115	26	32	16
Controls	117	19	38	13

animals were killed at the end of the eight months' period, the number of active tubercles was much less than that in the first group killed, and a number of tubercles were in the process of healing.

The incidence of tuberculous lesions in organs other than the lungs is shown in table 16. Only those animals are included in the total number of gassed animals and controls that lived long enough after inoculation to have an opportunity to develop tuberculosis. A number of both gassed animals and controls died within a few days after gassing or after inoculation—some from the effects of the gas, others from other causes. These are not included in the total figures, as they have no bearing on

the case, and would only obscure the issue. It would be difficult to tell from the table which were in better condition—the spleen, liver and kidneys of the gassed animals, or those of the controls. There was slightly more tuberculosis of the spleen and kidneys in the gassed animals, while the liver was invaded more often in those that were not gassed.

Table 17 shows the incidence of lung involvement in the animals that were gassed and in those that were not gassed. It was exactly the same in the two sets of animals. However, when the total number of lobes involved were studied, it was seen that the tuberculosis was more extensive in the controls than in the gassed animals.

Several interesting chance observations were made while studying the many microscopic sections from the animals used in these experiments. These are shown in figures 1 to 8. They represent various stages in an invasion of vessel walls by tubercle, and are interesting in relation to the development of acute miliary tuberculosis. Figures 1

TABLE 17.—*Incidence of Lesions in the Lungs and in the Lobes of the Lung*

	Total Number	Total Number with Lung Involvement	Total Number of Lobes Involved
Gassed animals	115	112	392
Controls	117	113	421

and 2 show small veins almost completely surrounded by tubercles. Figure 3 shows tuberculous involvement of an arterial wall, while figures 4 to 8 show tubercles which have broken through the walls of arteries and veins and have projected themselves into the lumen of the vessel. In one of the latter the tubercle is still covered by the intima of the vessel, while in the others the intima also has been broken through, and the tuberculous mass is washed constantly by the passing stream of blood.

That lesions of this type are not rare is well indicated by the textbooks of pathology. Adami and Nicholls,[71] in discussing miliary tuberculosis, state: "The condition often arises from the discharge of a caseating lymph-gland into a vein or from tuberculosis in the neighborhood of the receptaculum chyli and thoracic duct."

Delafield, Prudden and Wood[72] make the following statement: "A general infection may occur by the diffusion through the body of bacilli derived from a local tuberculosis, such as tuberculosis phlebitis or arteritis, or tuberculous inflammation of the thoracic duct."

71. Adami, J. G., and Nicholls, A. G.: Principles of Pathology, Philadelphia, Lea & Febiger, ed. 2, 1911, p. 318.

72. Delafield, F.; Prudden, T. M., and Wood, F. C.: A Textbook of Pathology, New York, William Wood & Company, 1921, p. 282.

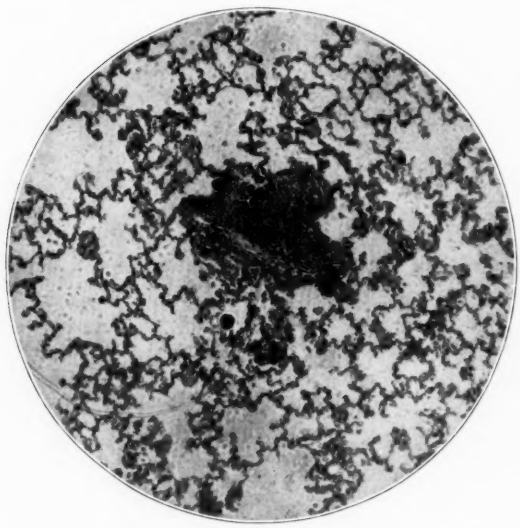

Fig. 1.—Tubercle partially surrounding a small vein. Animal killed thirty-nine days after inoculation.

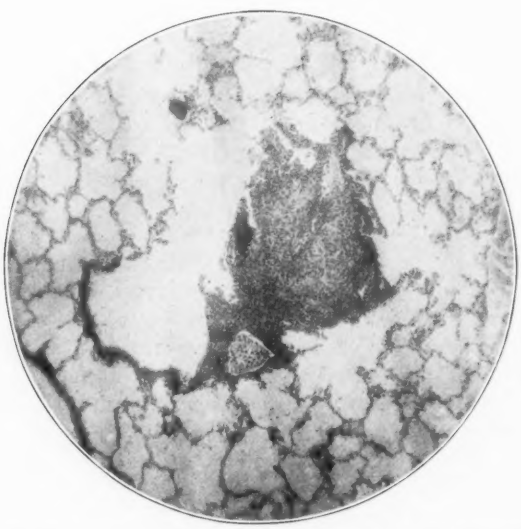

Fig. 2.—Small vein almost completely surrounded by tubercle. Animal killed thirty-five days after inoculation.

Fig. 3.—Tubercle of arterial wall. Animal killed thirty-five days after inoculation.

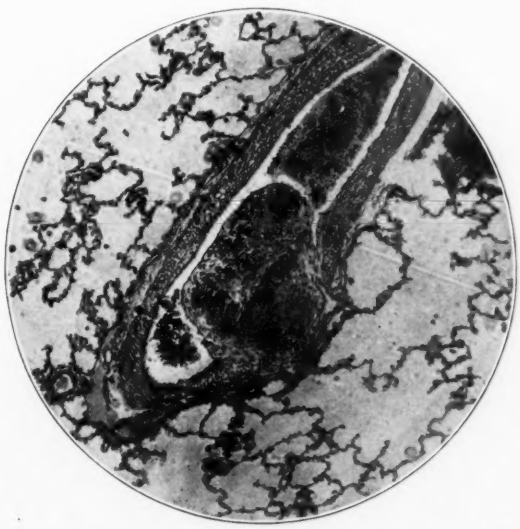

Fig. 4.—Tubercle projecting into the lumen of an artery. Note that the tuberculous mass is still covered by intima. Animal killed thirty-nine days after inoculation.

Fig. 5.—Tubercle projecting into lumen of a vein. There is a complete break in the wall of the vein, intima included, so that the tuberculous mass can be freely washed by the blood stream. Animal killed forty-two days after inoculation.

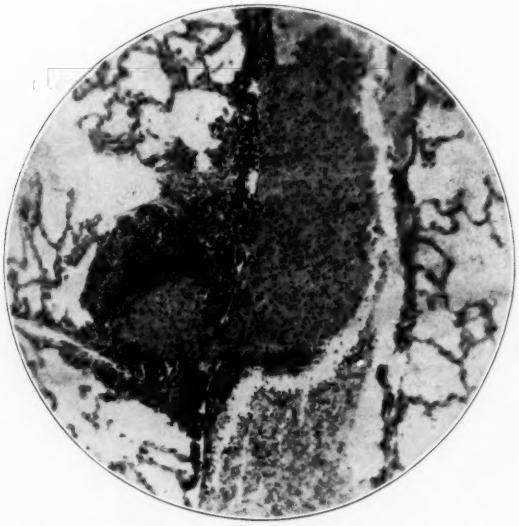

Fig. 6.—Higher power magnification of figure 5.

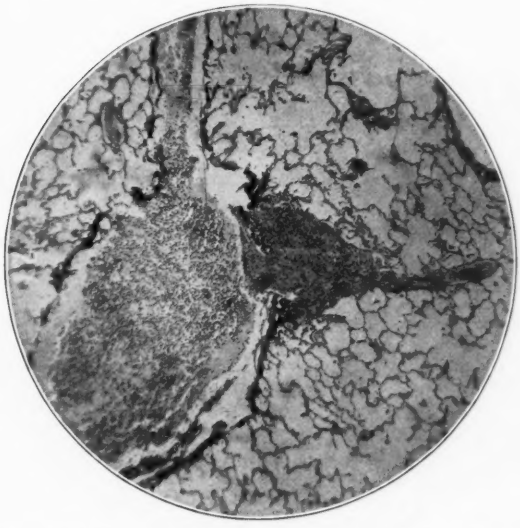

Fig. 7.—Tubercle projecting into the lumen of a vein. Complete break in vein wall, including intima. Animal killed forty-two days after inoculation.

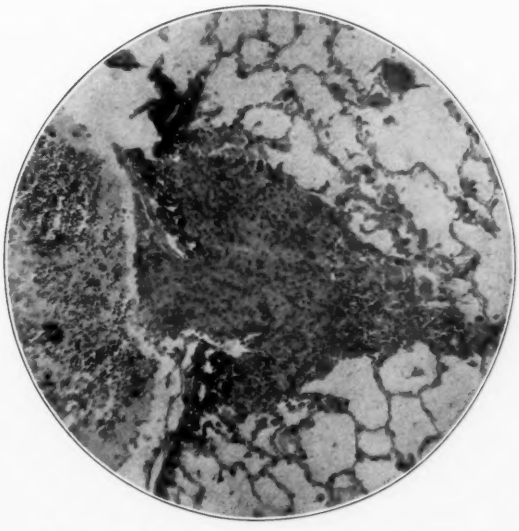

Fig. 8.—Higher power magnification of figure 7.

MacCallum,[73] in speaking of the focus of dissemination of bacilli in acute miliary tuberculosis, says:

> It is perhaps most usual to find the portal of entry in a branch of the pulmonary vein, ... and it proves especially common to find that a caseous lymph-gland attached by adhesion to the vein-wall is the source of the material. When the vein is laid open in the right place, it is found to be partly obstructed by a granular, cheesy mass, projecting into its lumen in such a way that the soft, bacillus-laden material is washed by the passing stream into the general current, or else there is a hole in the wall opening into a cavity in an adherent caseous tissue from which the bacilli are swept by an eddy of the stream out into the vessel. The discharge of the bacilli in either case is soon limited by the deposit of a protective covering of thrombus material on the exposed surface.

He states further:

> The distributing tuberculous lesion may be found on the endothelial lining of the vessel (or even through the entrance of bacilli into the vasa vasorum), and set free new and abundant bacilli only when it has become caseous. This is especially true of the thoracic duct, which receives bacilli through its branches and comes in time to be lined with caseous, ulcerating areas from which newly grown bacilli are poured off into the blood. Rarely one may find tuberculous caseous lesions in the heart discharging bacilli into the blood. Intimal tubercles and erosions in the aorta and smaller arteries are uncommon, and distribute their bacilli into a limited area only.

Finally, in 1905, Silvergleit [74] was able by careful searching to find a vascular tubercle in 95 per cent of the cases of miliary tuberculosis studied by him. It was most frequently located in the pulmonary vein, but was occasionally found in the thoracic duct, aorta and other vessels.

In spite of the comparative frequency of lesions of this type, as exemplified by published accounts, they seemed to me to be uncommonly enough seen in the course of the day's work to justify my giving them a passing consideration in this article.

CONCLUSIONS

These experiments demonstrate clearly that rabbits gassed with phosgene, mustard and lewisite are not more susceptible to tuberculosis than are control animals inoculated at the same time with the same dose of bacilli. The gassing of animals that already have well developed tuberculosis does not appreciably accelerate the tuberculous process. The sum total of the amount of tuberculosis in all the experiments was slightly less in the gassed animals than in the controls.

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73. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, ed. 2, 1921, p. 654.

74. Silvergleit, H.: Beiträge zur Entstehung der akuten allgemeinen Miliartuberculose, Virchows Arch. **179**:283, 1905.

PERIARTERITIS NODOSA

WITH SPECIAL REFERENCE TO THE ACUTE ABDOMINAL MANIFESTATIONS: REPORT OF TWO CASES *

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The direct relationship between the knowledge of the manifestations of a certain disease and the frequency with which it is recognized is well exemplified by the morbid condition known as periarteritis nodosa. Between the time the disease was first described by Kussmaul and Maier [1] and the date of publication of Schreiber's [2] review of the literature in 1904, a period of thirty-eight years, only fifteen additional cases had been recorded in medical archives. The authentic cases gathered by Ophüls [3] in 1923 totaled seventy, which number represents an additional fifty-three reported within a space of nineteen years. The recent summary by Gruber [4] of the cases found in the literature includes a description of 117 reports, to which may be added one by Frommel,[5] four by Christeller,[6] one by Paul,[7] five by Arkin [8] and two by me, bringing the total up to 130, an increase of sixty within three years. The increased number of case reports within the past few years points *a priori* to a more widespread and thorough knowledge of the character of the malady rather than to a more frequent occurrence of the disease.

Periarteritis nodosa has aroused greater interest and attracted more attention on the continent of Europe than elsewhere, due in part to the fact that the disease was first described and studied in Germany, but more especially to the circumstance that a considerably larger number

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1. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eingenthümliche Arterienerkrankung (Periarteriitis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484, 1866.

2. Schreiber, R.: Ueber Polyarteriitis nodosa, Inaug. Diss., Königsberg, 1904.

3. Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**:870 (Dec.) 1923.

4. Gruber, G. B.: Kasuistik und Kritik der Perarteriitis nodosa, Zentralbl. f. Herz. u. Gefässkrank. **18**:9-14, 1926.

5. Frommel, E.: L'arterite nodeuse, documents cliniques et anatomiques d'un cas nouveau, Ann. de méd. **19**:42, 1926.

6. Christeller, E.: Ueber die Lokalisationen der Periarteriitis nodosa besonders in den Bauchorganen, Arch. f. Verdauungskr. **37**:249, 1926.

7. Paul: Vereinigung der pathologischen Anatomen Wiens, Sitzung vom 26 April, 1926, Wien. klin. Wchnschr. **39**:1123, 1926.

8. Arkin, A.: Personal communication.

of postmortem examinations are held there. The importance of the autopsy in the recognition of the disease is readily appreciated when one learns that only 7 per cent of the cases have been recognized *intra vitam* (Mertens [9]). Besides the German and Austrian writers, many Hungarian authors have contributed to the voluminous literature on the subject which appears in German. In our language six reports of authentic cases are found in medical publications of England (Dickson,[10] Muir and Bruce,[11] Beattie and Douglas,[12] Cameron and Ludlow,[13] Carling and Hicks [14] and Wordley [15]) and thirteen in medical journals of the United States, including the two cases to be reported in this article.

The first case of periarteritis nodosa to be reported in this country is one from Osler's medical service at Johns Hopkins Hospital by Sabin [16] in 1901. Although the symptoms were similar to those described in the cases previously reported, the two excised skin nodules instead of presenting evidence of periarteritic inflammation were composed entirely of lime salts. Since autopsy was not permitted and conclusive proof of the presence of the disease is lacking, this case is not included in the thirteen here referred to. The first established case of periarteritis nodosa in the United States was reported by Longcope [17] in 1908. His publication was followed in 1911 by the respective reports of Cooke [18] and Lewis,[19] describing cases observed also in Philadelphia. Lamb [20] reported two cases in 1914, and Klotz' [21] article concerning two additional cases appeared in 1917. The reports of

9. Mertens, E.: Ueber Periarteriitis nodosa mit Massenblutung ins Nierenlager, Klin. Wchnschr. **1**:1841, 1922.

10. Dickson, W. E.: Pathological Society of Great Britain and Ireland, Meeting of Jan. 12, 1907, Lancet **172**:226, 1907.

11. Muir and Bruce: Pathological Society of Great Britain and Ireland, Meeting of Jan. 12, 1907, Lancet **172**:226, 1907.

12. Beattie, J. M., and Douglas, M.: A Case of Polyarteritis Acuta Nodosa, J. Path. & Bact. **17**:195, 1912.

13. Cameron, H. C., and Ludlow, P. P.: A Case of Periarteritis Nodosa, Guy's Hosp. Rep. **69**:159, 1918.

14. Carling, E. R., and Hicks, J. A. B.: A Case of Periarteritis Nodosa, Lancet **204**:1001, 1923.

15. Wordley, E.: A Case of Cortical Necrosis in the Kidney with Polyarteritis Acuta Nodosa, Lancet **205**:927, 1923.

16. Sabin, F.: A Case of Arterial Disease Possibly Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **12**:195, 1901.

17. Longcope, W. T.: Periarteritis Nodosa, Bull. Ayer Clin. Lab. Penn. Hosp., Philadelphia **5**:1, 1908.

18. Cooke, J. V.: A Case of Periarteritis Nodosa, Proc. Path. Soc. **14**:96, 1911.

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Ophüls,[3] Manges and Baehr,[22] Harris and Friedrichs [23] and of Keegan [24] followed in the order given.

Due to the fact that more than nine tenths of the cases of periarteritis nodosa are not recognized until the time of autopsy and at times not until microscopic sections of the postmortem material are studied, most of the detailed reports in the literature are furnished by pathologists, with only a brief summary of the clinical data. As Sacki [25] observes, the disease is disposed of in textbooks and systems of internal medicine in a few lines, whereas in treatises on pathologic anatomy lengthy and detailed descriptions are accorded the subject. On this account it is deemed advisable to stress the clinical side of the two cases reported in this article in spite of the fact that far more study was expended on the pathologic material. A second and perhaps more cogent reason for emphasizing the clinical aspect of periarteritis nodosa is that a better knowledge of its perplexing symptomatology will unquestionably lead to a more frequent and earlier recognition of the disease, which is essential to the elucidation of its etiology. At present the opportunity for the search of the causative agent at the most favorable time, that is, at the beginning of the disease, is rarely afforded the clinician or the laboratory worker, since the underlying condition is first discovered, as a rule, at autopsy.

REPORT OF CASES

CASE 1.—*History.*—J. S., a man, aged 29, was admitted to the medical service of the Cook County Hospital on Oct. 7, 1923, complaining of epigastric pain, jaundice, epistaxis and melena. The onset, dating back five weeks, was insidious, with constipation, anorexia, occasional vomiting and epigastric distress. The abdominal discomfort was of a dull continuous type subject to acute exacerbations in the form of a cramplike pain. Two weeks before entrance, the patient noticed that his sclerae were jaundiced. At this time he experienced, in addition to dimness of vision, xanthopsia and headache. Three days prior to admission he was seized with severe epigastric cramps which led him to resort to an enema, following the introduction of which large masses of clotted blood were passed. Nosebleed occurred for two hours on the day of the hemorrhage from the bowel and recurred for a longer period the day preceding the patient's admission to the hospital.

In a general inventory of symptoms by systems, nocturia four to five times a night and urgency of urination were elicited. His past history indicated the occurrence of an attack two years previous similar to the present one except for the absence of jaundice. He admitted a Neisserian infection and a hard chancre fifteen and ten years ago, respectively.

Physical Examination.—This disclosed a well developed colored man with marked jaundice of the sclerae and mucous membranes. The essential observa-

22. Manges, M., and Baehr, G.: Periarteritis Nodosa, Am. J. M. Sc. **162**:162, 1921.

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24. Keegan, J. J.: Primary Vascular Nephritis or Renal Periarteritis Nodosa, Arch. Int. Med. **36**:189 (Aug.) 1925.

25. Sacki, F.: Zur Klinik der Periarteriitis nodosa, Med. Klin. **20**:44, 1924.

tions consisted of an enlargement of the heart, mainly to the left, and a systolic murmur heard best over the apex and widely transmitted. The upper margin of the liver was found, on percussion, to be in the fourth interspace; the lower border, two fingerbreadths below the costal margin. Tenderness was elicited in the epigastrium. A generalized superficial adenopathy of slight degree was present. The blood pressure was 200 systolic and 140 diastolic.

Laboratory Observations.—Urinalysis showed the presence of bile and albumin. The white blood count was 11,000, and 4 per cent of the cells were eosinophils. The red cell count was 2,260,000, and the coagulation time (watch crystal method) was three and one-half minutes. The stool apparently contained bile pigment, for it was light brown.

Diagnosis.—Following the admission of the patient, the diagnosis rested between a catarrhal jaundice and a diffuse syphilitic hepatitis. In addition, a chronic nephritis with consequent hypertension and cardiac hypertrophy were assumed to be present.

Subsequent Course.—The visible jaundice subsided somewhat, the stools became darker, and the urine showed less bile. Repeated attacks of epigastric pain associated with nausea and vomiting, however, kept the patient in an uncomfortable state.

On October 25, the following notation was made: "The patient has been having considerable localized epigastric pain of a severe cramplike nature and has vomited twice this morning. There is moderate tenderness and resistance in the right infracostal region. The acute cramplike pain suggests the presence of a biliary stone which is causing incomplete obstruction."

Repeated hemorrhage from the nose and bowel was a prominent feature throughout the course of the disease. The degree of jaundice varied. The epigastric pain, at times only slight, was practically continuous.

The notation recorded on October 30, reads: "The course of the illness points to a duodenal ulcer associated with cholecystitis and local peritonitis. The possibility of a perforation of the gallbladder into the stomach or duodenum should be considered. The hypertension of 200 mm. in an individual 29 years of age is due most likely to an underlying nephritis, to which the ulcer, if present, might be related; the absence of retention of nonprotein nitrogenous substances would render a nephritic origin of a gastric or duodenal ulcer unlikely." The patient was placed on the Sippy treatment for ulcer, but failed to respond to the antacid therapy.

Pain was the most outstanding feature of the clinical picture, although it varied greatly in degree. After a sleepless night due to epigastric cramps, on November 6 the patient had an attack of such excruciating pain as to cause him to cry out. Surgical intervention was deemed advisable, and the patient was transferred to the surgical service.

The laboratory observations, in addition to those recorded at the time of entrance, included two negative blood Wassermann tests, gastro-intestinal roentgen-ray examination which failed to demonstrate the presence of any lesion, an Ewald test meal with an acidity of 68 free and 92 total, and a positive test for chemical blood. No food particles or raisins were recovered six hours after the ingestion of a motor meal. The daily urinary output varied between 740 and 2,500, averaging about 1,300 cc. The specific gravity of the urine was fixed, being recorded constantly as 1.008 or 1.010. Albumin and casts were reported in most specimens. Chemical examinations of the blood (three) failed to show a consistent degree of retention. Successive blood counts showed the presence of a high grade secondary anemia, the red count ranging between 1,245,000 and 1,870,000. A single blood culture yielded staphylococci which were assumed to be contaminating organisms. The temperature throughout the course was subfebrile, usually between normal and 99.6 F. The pulse rate averaged from 80 to 90 beats per minute, and the respiratory rate was, as a rule, between 24 and 26.

Surgical Service Date.—The day following his arrival in the surgical ward (Nov. 7, 1923), the patient developed hematemesis, an occurrence which further complicated the picture. The preoperative summary made by the surgeon reads: "In view of the history of attacks of pain simulating gallbladder colic, and findings of jaundice of an obstructive type, a palpable mass in the right upper quadrant, leukocytosis and a low grade temperature, rupture of an empyema of the gallbladder into the duodenum is suspected. The hemorrhages may be due to the cholemic state or to a hemorrhagic diathesis dependent on the underlying disease process. The prognosis in view of the presence of a high grade anemia is grave."

At the operation, performed on Nov. 8, 1923, the gallbladder was bound by dense fibrous adhesions to the pyloric portion of the stomach and duodenum. When the fundus of the gallbladder was separated from the duodenum, a defect in the serosa of the latter was discovered but was not probed. Infiltration about this point was not felt. The gallbladder when in situ was considered to be filled with blood, as was also a limited portion of jejunum. There were multiple adhesions of the small intestines. The defect in the duodenum was repaired and the gallbladder extirpated. The diagnosis at operation was Henoch's purpura.

With the aid of hypodermoclysis and blood transfusion, the patient passed through a rather uneventful convalescence. On the thirteenth day after operation, Nov. 21, 1923, the patient left the hospital feeling greatly improved.

Readmission to the Hospital.—The patient returned to the hospital on Feb. 21, 1924, exactly three months after the date of his discharge; on this occasion he was admitted to another medical service. Subsequent to the time of his discharge, he was apparently improved, according to his mother, but he was suffering from inconstant recurrent attacks of mild epigastric pain which only occasionally became sharp. The icterus, headache and constipation had been greatly relieved, whereas evidences of hemorrhage had entirely disappeared. About a month following the operation, shortness of breath manifested itself; this increased gradually, and was accompanied by a subcutaneous edema spreading from below upward. The semicomatose state in which the patient was seen at the time of entrance had been present since the previous day.

The physical observations were those of a myocardial insufficiency, the dependent edema being high grade. The urine, which had a specific gravity of 1.026, contained a moderate amount of albumin, many red and a few white cells and many hyaline and granular casts. The systolic blood pressure measured 152 mm.; the diastolic, 130 mm.

The diagnosis of the presenting condition was given as broken compensation secondary to chronic diffuse nephritis. The patient died within twenty-four hours after entering the hospital; therefore this became a coroner's case. Autopsy was not performed by the coroner's physician.

Summary of Clinical History.—A colored man, aged 29, was stricken with anorexia and constipation followed by colicky epigastric pain at times associated with vomiting. Deep jaundice and its concomitants followed, also repeated attacks of epistaxis and melena. The unrelated symptom of nocturia was traced to a chronic nephritis, as determined by laboratory methods. The blood pressure was 200 systolic and 140 diastolic. Severe attacks of pain in the upper part of the abdomen led to the diagnosis of cholecystitis, associated perhaps with a duodenal ulcer. The symptomatology referable to gallbladder disease dominated the picture to such a degree that in spite of the severe anemia developed as a result of the epistaxis, melena and hematemesis which rendered the patient a poor surgical risk, operative intervention was considered indicated. At the operation the jejunal content was seen to be hemorrhagic and a gallbladder distended by blood was removed. The patient died three months later with evidence of myocardial insufficiency secondary to a chronic nephritis.

Pathologic Report.—Gross examination of the extirpated gallbladder submitted to the central laboratory revealed a recently removed gallbladder and a mass of clotted blood. The gallbladder, which had been opened, measured 9 cm. in length and had a maximum circumference of 9.5 cm. The serous coat was roughened in places by fibrous tags, its color was pale pinkish red with dark blue circular spots scattered here and there over its surface. These dark spots corresponded in location to firm nodules measuring from 2 to 4 mm. in diameter which were located within the wall of the gallbladder. When some of these nodules were sectioned, they were seen to consist of thrombi distending and occluding the finer arteries coursing the muscularis. Along one margin of the gallbladder was a firm cordlike structure about 2 cm. in length, which on cross-section was seen to be a thickened, occluded vessel, from its position presumably the cystic artery. The thickness of the wall of the gallbladder was increased owing to edema, mainly of the muscularis, which was the seat of the thrombotic nodules described in the foregoing. The mucosa, which was intact and normally smooth, was covered in its proximal half by a dark brown, somewhat viscid material probably representing an admixture of bile and altered blood. When the mucosa was washed free, it appeared pale except for scattered dark blue spots shining through its surface similar in appearance to and corresponding in location with the subserous nodules which have been described. No bleeding point was demonstrable. The clotted blood consisted of one mass which formed a cast of the distal half of the gallbladder and several other disorganized smaller pieces. The peripheral portion of the large clot was rather dry and pinkish red, the central part a deep purplish red. A lymph gland measuring 1 by 1 by 0.5 cm. attached to the proximal portion of the gallbladder was fleshy pink, soft and enlarged.

The microscopic description of a section through one of the bluish red nodules reads: There was a marked disproportion between the size of the channel and the thickness of the vascular wall, apparently due to an aneurysmal dilatation of the artery. The lumen was completely occluded by an organizing thrombus exceedingly rich in young granulation tissue and capillaries. Most of the vessel wall was destroyed, rendering identification of the individual layers practically impossible. The outer layers of the vessel and the indefinitely demarcated surrounding fibrous tissue were infiltrated by round and plasma cells, together with a small number of leukocytes. A lymph gland taken from the region of the cystic duct showed a diffuse increase of lymphoid cells and large cortical follicles with distinct germinal centers.

The diagnosis submitted at the time was that of an infectious arteritis with multiple aneurysmal dilatations and consequent thromboses. It was not until later when the changes described in the foregoing were recognized as part of the pathologic entity—periarteritis nodosa—that the explanation of the bizarre symptomatology became apparent.

Case 2.—*History.*—J. F. O'C., a man, aged 57, was admitted to the Cook County Hospital on Dec. 1, 1925, with complaints referable mainly to a decompensated heart. Shortness of breath, particularly marked on exertion, had been noted for eight months previous to admission. The swelling of his lower extremities had been noticed for only one month, whereas the scrotal edema which the patient presented became apparent the previous day. He also complained of dizziness on exertion, slight cough, and, occasionally, palpitation. Further questioning elicited the presence of nocturia. In the past history it was stated that the patient had had a grippal infection thirty years before and gonorrhea twenty-five years ago. The patient said that he had not had syphilis.

Physical Examination.—This revealed a well nourished white man, somewhat dyspneic but not acutely ill. The temperature was 97 F., the pulse rate 100 and the respiratory rate 26. The blood pressure was 200 mm. systolic and 100 mm. diastolic. The heart was enlarged and the tones indistinct, but no actual murmurs were heard. Râles were audible at the bases of both lungs; the liver

extended two fingerbreadths below the costal margin and was tender; there was evidence of fluid in the abdomen and of a pitting edema of the lower extremities.

Laboratory Observations.—The urine showed the presence of albumin and hyaline casts; the blood chemistry indicated some retention of the noncoagulable nitrogenous elements of the blood (nonprotein nitrogen 53.3, urea 66.96, and creatinine 2.75). The blood Wassermann test was negative, and the electrocardiographic tracing did not show any significant changes.

Diagnosis.—The condition was considered an old nephritis with secondary hypertension and myocardial insufficiency.

Subsequent Course.—Following the usual therapeutic measures the patient improved, and he was discharged on Dec. 17, 1925, being referred for further observation and treatment to the heart clinic of the University of Illinois College of Medicine dispensary. After a month of ambulatory treatment, it was found necessary to hospitalize the patient on account of dyspnea.

First Admission to Research and Educational Hospitals.—Except for the almost complete disappearance of dyspnea, the patient in general presented the same picture described previously. His blood pressure at this time was recorded as 238 systolic and 128 diastolic. The nonprotein nitrogen was determined to be 110 mg., and creatinine 2.4. The Mosenthal test showed a variation of only two points in the specific gravity of the day specimens. The total day urine measured 471 cc. and the night urine 855 cc., with a specific gravity of 1.021. The phenolsulphonphthalein test showed an output of 15 per cent during the first half hour and a total output of 43 per cent in two hours. The urine showed a slight amount of albumin, an occasional granular and a few hyaline casts. The blood examination showed the presence of a secondary anemia with a leukocyte count of 11,400. The patient left the hospital after a stay of only four days but was readmitted on March 18, 1926.

Second Admission.—The patient at this time presented symptoms similar to those previously noted. The blood pressure was recorded as 245 systolic and 130 diastolic; the heart tones were distant, but no irregularities or murmurs were heard. A slight edema of the scrotum was present. The phthalein test showed an output of 7 per cent of dye in the first hour and an additional 8 per cent in the second hour. The Mosenthal test yielded results similar to those recorded during the previous stay. The blood count on March 19, 1926, was 21,350, of which 83 per cent were polymorphonuclear leukocytes. The first record of abdominal complaint, which was subsequently and frequently repeated, was noted by the nurse on March 19. On the 21st, it was stated that the patient was restless, and on the 27th delirum was at times manifested. On March 30, the patient developed severe pain in the right upper quadrant of the abdomen, which was described as cramplike, and was apparently excruciating. The picture presented suggested a surgical lesion, and consultation was requested.

The following notes dictated by the examining surgeon indicate the observations at that time: "There is spasm and some tenderness in the right upper quadrant chiefly. The abdomen is distended and held rigid. The patient is semidelirious and cannot be made to relax. Gallbladder disease is most likely present, although the possibility of appendicitis must be borne in mind. In view of the uncertainty of the diagnosis and the mental condition of the patient, further observation is desired and expectant treatment recommended."

On the following day the tenderness and rigidity had diminished, but there was slight increase in the distention of the abdomen. A slight icterus appeared which vacillated in degree throughout the remainder of the course of illness. The patient was again seen about two weeks later by the surgeon who still felt inclined to defer operation, mainly on account of the mental condition of the patient. A previous flat film had shown no pathologic shadows in the upper right quadrant. Roentgenograms of the gallbladder region made on April 12

after the oral administration of sodiumtetraiodophenolphthalein did not show any definite gallbladder shadow. Repetition of the Graham-Cole procedure at a later date gave identical results.

The bromsulphalein test performed for a month at intervals of about one week showed the presence on the average of 30 per cent of the dye in the blood serum thirty minutes after injection. The icterus index determined April 1 was 25, and the van den Bergh test showed a direct positive reaction with the presence of 2.8 mg. of bilirubin per hundred cubic centimeters of blood. On April 14, the icterus index had dropped to 11.5; the van den Bergh gave a diphasic reaction and quantitatively 1.8 mg. per hundred cubic centimeters.

The patient became progressively weaker and developed, in addition to the evidences of nephritis, abdominal symptoms and delirium, definite signs of a polyneuritis. On May 15, it was noted that the patient had a wrist-drop on the left and a foot-drop on the right side, together with the inability to flex the index finger of the right hand. In the final stages he developed signs of fluid in the chest and abdomen, became more and more stuporous and passed into a deep coma on May 25, in which he died.

The temperature remained normal or subnormal until April 31, when 100.2 F. was recorded on rectal measurement. Following this time the fever curve fluctuated irregularly, at no time rising above 101 F., usually averaging from 99 to 100 F. The curve frequently fell below the normal level, and on one occasion remained there for a period of three days. The pulse rate was at times disproportionately rapid, but for the most part its oscillations corresponded with those of the fever curve. The average pulse rate was between 100 and 120. Repeated blood counts showed the presence of a leukocytosis of variable degree. The white count rose from 20,000 at the time of entrance to 44,000 on April 2, to drop and rise again, and finally to fall once more to 19,000 recorded the day preceding death. Differential counts showed a polymorphonuclear leukocytosis ranging between 83 and 93 per cent, of which at no time did eosinophils constitute more than 2 per cent. The Wassermann test of the blood was negative. Blood cultures remained sterile.

Since the clinical facts in the case would not sustain any single diagnosis suggested and the combination of a number of different diseases seemed unlikely, it was deemed advisable by the clinicians to be guilty of an error of omission rather than commission and to send the patient to autopsy with a diagnosis of morbus incognitus.

Autopsy.—The autopsy was performed by Dr. R. H. Jaffé, from whose complete protocol the following excerpts were taken. In order to conserve space, only a brief summary of the essential observations made during the pathologic examination is included in this report.

The only alteration in the heart referable to the vascular disease was a thickening of the branches of the left circumflex coronary artery, with marked narrowing of the lumens of some. In order to detect these lesions it was necessary to examine the vessels with great care.

In the liver a network of scars was seen in the capsule, and on section, whitish linear markings separating unilobular and multilobular dark red areas were found. In the middle of the left lobe, 7 mm. below the capsule, was a spherical, dark red nodule 9 mm. in diameter, consisting of blood in the center surrounded by a grayish-white capsule.

Striking changes were found in the gallbladder (fig. 1). On section of its wall, the enormously thickened cystic artery (*A*) was exposed to view. After removal of several pigment stones and a cloudy yellow bile, the lining of the gallbladder was seen to present a branching system of linear elevations (*B*) stained green mottled with yellow, representing apparently thickened blood vessels in which were foci of necrosis (*C*). In places, slight nodular enlargements were discerned. A few dark red hemorrhages were found in relationship to and distant from the involved vessels.

In the pancreas also the changes were remarkable. On section the pancreatic tissue was seen to be grayish-white with several subcapsular, more or less triangular, dry, opaque, yellowish-white areas (anemic necrosis), averaging about 8 mm. in diameter, often surrounded by firm grayish-red zones. In the fat tissue about the head of the pancreas the smaller arteries were thickened, and their walls were firm and indurated.

The surface of the right kidney was uniformly granular, the regular grayish-white elevations being separated by deep grayish-red depressions. The cut surface was mottled grayish red and white, obliterating the normal renal markings. The medulla was pale as compared with the cortex. The sectioned vessels presented thickened walls and gaping mouths. The left kidney showed the same changes as the right, and in addition, a yellowish-white, wedge-shaped subscapular area about 5 mm. at the base, located near the upper pole.

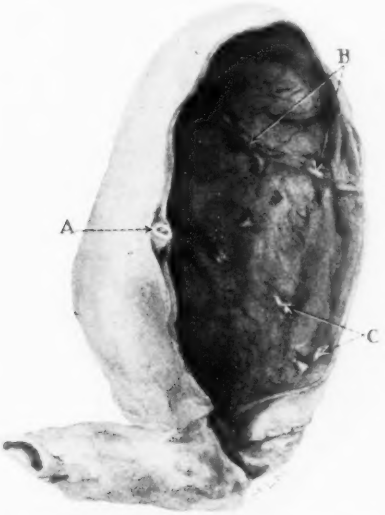

Fig. 1.—The opened gallbladder exposing a cross-section of the greatly thickened cystic artery (*A*) and a network of linear elevations (*B*) representing the thickened branches of the cystic artery. The lighter areas (*C*) are foci of necrosis corresponding to the sites of nodular thickenings.

Involving the vessels at the base of the brain was a marked sclerosis which extended also into the smaller branches.

The right peroneal and radial nerves on section showed no gross change. The intercarpal spaces on the dorsum of the right hand were conspicuous as compared with those of the left.

Microscopic Report.—Areas of complete atrophy of the cortical tissue in the kidneys alternated with regions in which the parenchyma appeared uninvolved. In the more or less intact areas the glomerular tufts were rich in nuclear elements and the endothelial cells swollen, but the capillaries had distinct outlines and contained red blood cells; the tubules here were distended and lined by swollen, clear epithelial cells. In the zones of atrophy which assumed the form of striations not sharply demarcated from the relatively normal tissue, the glomeruli were hyalinized and the tubules diminutive or replaced by proliferat-

ing stroma rich in round cells. All the arteries from the interlobar branches to the arterioles showed changes, the most severe alterations, however, being noted in the atrophic areas. The walls of the interlobar arteries were greatly thickened, mainly owing to a diffuse connective tissue increase which obscured the normal distinction of the adventitial, medial and intimal coats. The lumina of these vessels were extremely narrow, being for the most part filled with fibrous tissue. In the adventitia there were dense collections of cells consisting chiefly of eosinophilic and neutrophilic leukocytes, round and plasma cells and histiocytes which infiltrated and extended into the surrounding tissues. Similar changes and more acute alterations were observed in the arcuate arteries. Here one saw fibrinoid necrosis of circumscribed parts of vessel walls often

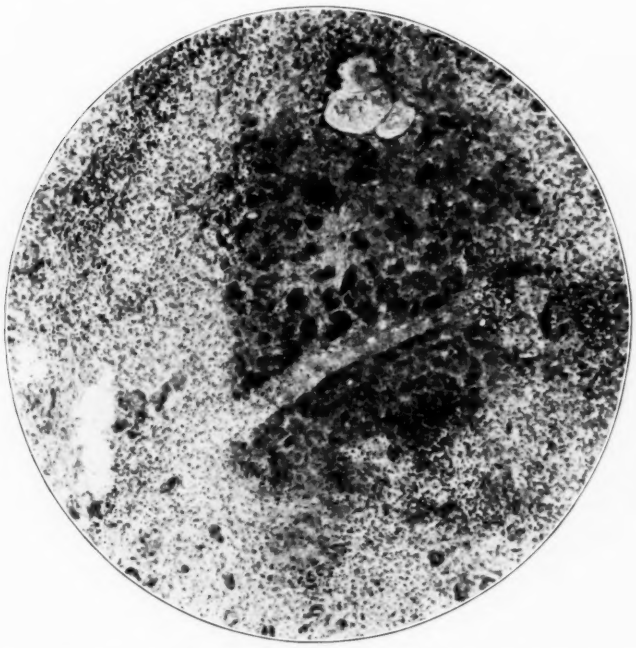

Fig. 2.—Circumscribed necrosis of the pancreatic parenchyma surrounded by a zone of inflammatory reaction. ×80.

involving the internal elastic membrane, remnants of which could still be identified. In some places, presumably the sites of origin of the interlobular branches, the walls were entirely necrotic. Here and there the infiltrations of eosinophils extended toward the inner coats of the vessel walls. The arterioles showed extreme hyaline thickening with deposition of lipoid. In the larger arteries the occlusion was apparently due to organized thrombi showing distinct canalization, whereas the medium sized and smaller arteries were narrowed as a result of proliferative changes of the intima.

There were circumscribed areas of necrosis in the pancreas in which the acini and fat cells were transformed into structureless masses. Each one of these foci of necrosis (fig. 2) were surrounded by a zone of inflammatory

reaction containing many eosinophilic leukocytes, round and plasma cells and fibroblasts. The acini in the region of reaction had lost their structure and the individual parenchymal cells their zymogenic granulation. There were also areas of scar formation, the fibrous tissue being cellular and containing shrunken epithelial cells filled with fat droplets. There was a normal preservation of the islets of Langerhans, the cells of which contained small fat granules. The arteries coursing through the thickened interlobular septums were markedly altered by a noteworthy intimal proliferation which had led to high grade, more or less eccentric narrowing of the lumina with at times irregular canalization (fig. 3). In some areas more recent changes represented by infiltrations of oxyphilic leukocytes and round cells were noted (*a*). These infiltrates, which

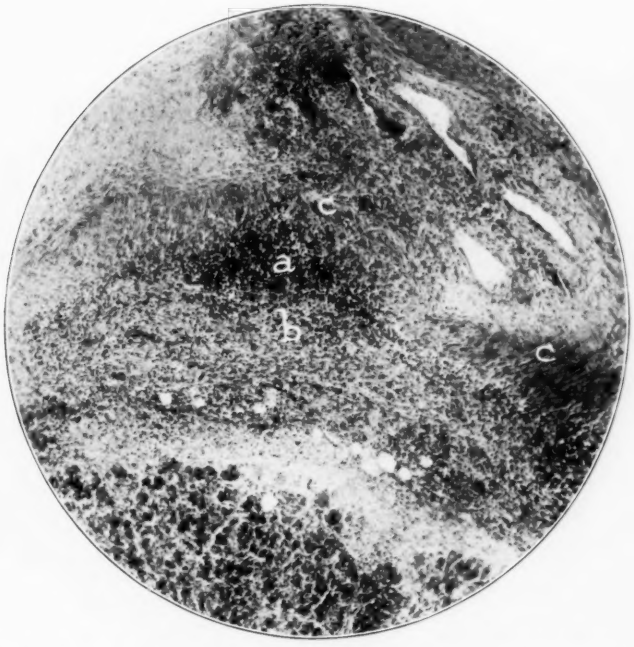

Fig. 3.—Irregular canalization of a medium-sized pancreatic artery. The periarterial infiltration is most marked at (*a*) where the inflammatory cells appear to extend from the adventitia (*b*) to invade the media (*c*). ×60.

appeared to have their origin in the adventitia and to have progressed toward the media, may have involved the entire circumference of the smaller arteries. In places circumscribed aneurysmal dilatations filled with blood clots were found adjacent to vessels the lumina of which were almost completely occluded.

The wall of the cystic artery (fig. 4), which was severely injured, was greatly thickened and its caliber correspondingly decreased. About one third of the lumen was occupied by a loose network of fibrin (*a*), in the meshes of which a number of leukocytes mostly with eosinophilic granulations were found. That portion of the internal part of the vessel wall immediately adjacent to the fibrinous deposit was composed of a coarse hyaline substance (*b*) which was limited to this area. In passing centrifugally, the hyalinized zone was found to

be separated from the external portions of the vessel wall by a cavity (*c*) (recanalization?) which was lined in the peripheral part by foamy cells (*d*) with golden yellow pigment granules (hematoidin in macrophages). In the remaining two thirds of the wall, a part of which is shown in figure 5, the internal layers consisted of fibrillar connective tissue, the fibers being arranged concentrically about the lumen (*a*). In the more peripheral layers, remnants of the elastica interna represented by a tortuous line (*b*) often broken up by the invading connective tissue could be identified. All that remained of the media (*c*) were a few smooth muscle fibers with thin elastic fibrils between them attached to the external surface of the inner elastic membrane. The enormously thickened adventitia (*d*) passed almost imperceptibly into the surrounding fibrous tissue (*e*).

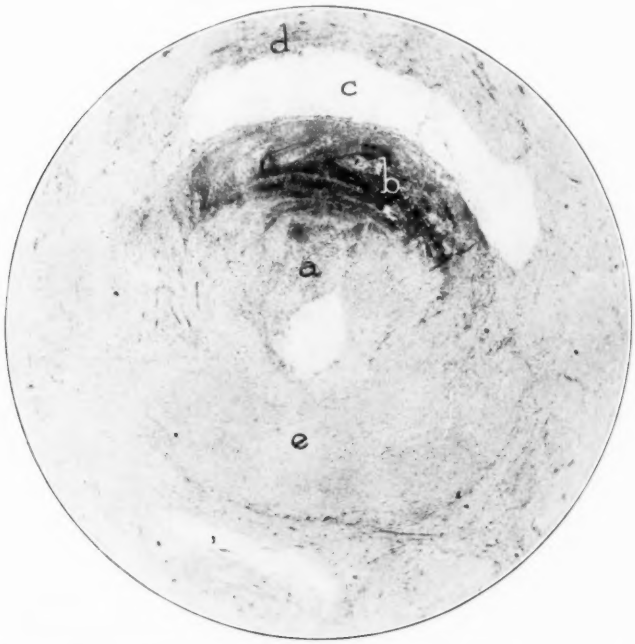

Fig. 4.—The greatly thickened wall of the cystic artery in cross-section. The present small lumen is partially occupied by a loose network of fibrin (*a*) in the meshes of which are many leukocytes. Adjacent to the fibrinous deposit is a coarse hyaline substance (*b*), external to which is a cavity (*c*) lined by macrophages (*d*) laden with hematoidin. The site represented in figure 5 is located at (*e*). ×24.

In the liver, the periportal connective tissue was increased in amount and tended to invade by extension the adjacent portions of the surrounding lobules. Infiltrations of cells were marked in these areas, as was also bile duct proliferation. The branches of the hepatic artery in general had suffered little injury. The nodule in the left lobe noted in the gross description consisted of a blood coagulum surrounded by a connective tissue capsule. The clot had a homogeneous hyaline center in which were embedded a few macrophages and

leukocytes the latter mainly oxyphilic. Peripherally there were fibroblasts and young capillaries, together with a greatly increased number of macrophages which contained a dark, yellowish-brown, blood pigment. The capsule consisted chiefly of fibrillar connective tissue and distended capillary vessels with, in one place, a few degenerated smooth muscle fibers. In the more external layers were found well circumscribed, small foci of infiltrated round cells and eosinophilic leukocytes. The nodule was embedded in a dense connective tissue supporting several medium sized arteries with thick walls and narrow lumina.

The most conspicuous change in the prostate was found on cross-section of an artery (fig. 6) which was of far greater caliber than would correspond to the thickness of its wall. The lumen of the vessel was apparently distended by a blood clot

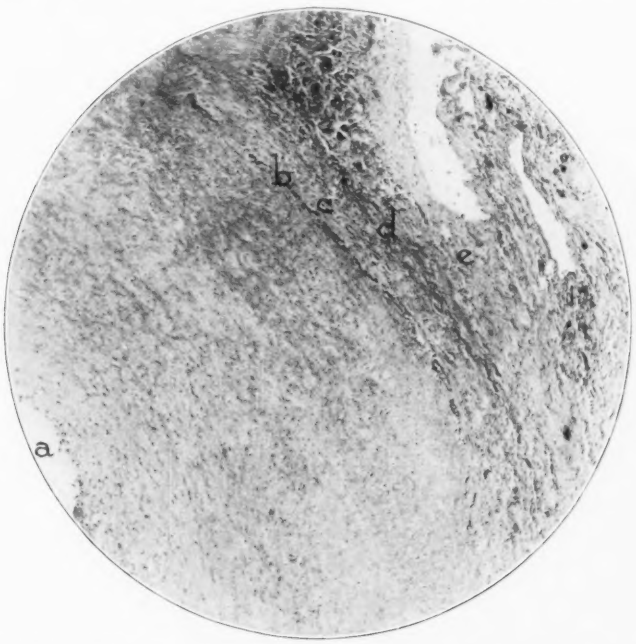

Fig. 5.—A higher magnification of that portion of the wall of the cystic artery designated by (*c*) in figure 4 (Weigert's elastica stain). About the lumen (*a*) are concentric layers of fibrillar tissue, in the more peripheral parts of which are remnants of the elastica interna (*b*). The media (*c*) is partially destroyed but can still be identified. The enormously thickened adventitia (*d*) passes almost imperceptibly into the surrounding fibrous tissue (*e*). × 60.

interlaced with young capillaries and fibroblasts. Immediately about the artery there was considerable deposition of blood pigment both free and engulfed, and in close proximity (not included in the illustration) were several other thick-walled, almost completely occluded vessels separated by dense connective tissue containing pigment.

Many of the larger arteries of the heart did not show any change, although some revealed proliferation of the intima producing eccentric narrowing of the vascular channels. In the connective tissue about the vessels and in the sub-

epicardial fat tissue were circumscribed infiltrations composed of lymphoid cells and eosinophils, which extended between the muscle fibers.

In some of the bundles of the peroneal nerve evidence of severe injury was found. The myelin sheaths of the nerve fibers stained bright orange with sudan III, and in some places were broken up into droplets of varying sizes which were partly phagocytosed by histiocytes. The small arteries here had diffusely thickened walls surrounded by round cells which frequently invaded the outer coats of the vessel.

Hemorrhage and necrosis associated with the presence of severe vascular injury was noted in the testicle. In the areas of greatest involvement could be seen a diffuse fibrinoid degeneration with cellular infiltrations of the arterial walls and thrombosis of the lumina.

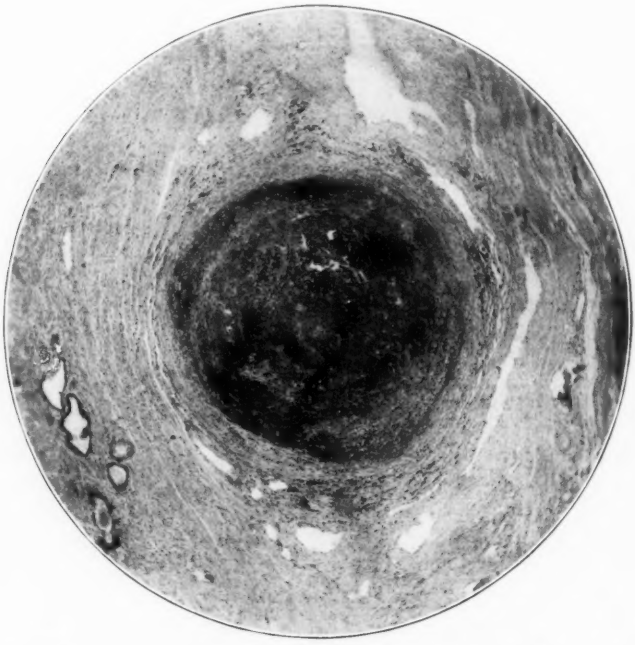

Fig. 6.—Section through a thrombosed aneurysmal outpouching of a prostatic artery. About the vessel wall is a heavy deposit of blood pigment both free and engulfed. × 36.

In the fat tissue surrounding the suprarenal and the fibrous tissue about the thyroid were striking alterations in the blood vessels, around which were nodular accumulations of round cells and eosinophilic leukocytes. Within these glands the changes affecting the arteries were less marked.

In the spleen, the malphigian bodies presented distinct germinal centers, while the pulp showed diffuse thickening of the reticulum and sinuses of medium width filled with blood. In the trabeculae were many eosinophils and plasma cells. The walls of the smaller arteries were sclerotic and hyalinized.

The vessels in the brain were extensively involved by atherosclerosis presenting, even on careful search, no evidence of inflammatory change.

ETIOLOGY

A great deal of interest has centered about the etiology of the malady. A consideration of the evidence pro and con in connection with various views is beyond the scope of this paper. It is generally agreed, however, that periarteritis nodosa is an infectious disease, although the causal organism has not been identified. Investigations carried on in connection with a corresponding condition occurring in deer has failed to shed any light on the causation of the disease (Lupke,[26] Jaeger [27]). The study of similar cases in a calf (Guldner [28]) and a pig (Joest [29]) likewise led to negative bacteriologic results. Cameron and Ludlow [13] suggest a parasitic origin on the basis that multiple aneurysms occurring along the mesenteric vessels in horses is known to be due to the parasite *Strongylus armatus*. What is more significant, these authors state, is a case of aneurysms in dogs studied by Haythorn and Ryan,[30] in which it apparently was established that the aneurysms were produced by a nematode worm, *Spirocerca sanguinolenta*. The eosinophilia found at times in man in periarteritis nodosa may be a point in favor of the parasitic theory.

Harris and Friedrichs [31] (who give a complete summary of the etiology of periarteritis nodosa) have succeeded in reproducing lesions in rabbits similar to those occurring in man, and have adduced a great deal of evidence in support of their claim that a filtrable virus is the cause of the disease. In his latest review of periarteritis nodosa, Gruber,[4] after weighing the facts thus far accumulated, stoutly defends the notion that this condition is not a disease *sui generis*, but that it may be produced by a number of different agents, a view shared by most authors. It is the general consensus of opinion that syphilis plays no rôle in the production of the disease; it is therefore no longer accorded a place of importance in discussions of the subject.

PATHOLOGY

Since the nature of the disease as already stated is, as a rule, first recognized at the time of autopsy, opportunity for clinical study of periarteritis nodosa has been limited, whereas the pathologic side of the

26. Lupke, F.: Ueber Periarteriitis nodosa bei Axishirschen, Verhandl. d. deutsch. path. Gesellsch. **10**:149, 1906.

27. Jaeger, A.: Vergleichend—pathologische Untersuchungen über die Periarteriitis nodosa, Verhandl. d. deutsch. path. Gesellsch. **13**:209, 1908.

28. Guldner, E.: Zwei neue Beobachtungen von Periarteriitis nodosa beim Menschen und beim Hausrinde, Virchows Arch. f. path. Anat. **219**:366, 1915.

29. Joest, referred to by Guldner (footnote 28).

30. Haythorn, S. R., and Ryan, A. H.: Aortic Aneurysms in Dogs with the Report of Six Cases, J. M. Research **35**:411, 1916-1917.

31. Harris, W. H., and Friedrichs, A. V.: The Experimental Production of Periarteritis Nodosa in the Rabbit with a Consideration of the Specific Causal Excitant, J. Exper. Med. **36**:219, 1922.

subject has been considered in an exhaustive manner in numerous recent works (Gruber [4]). In view of the abundant literature, a detailed discussion of the morbid anatomy of the disease would prove superfluous. For a clear understanding, however, of the complicated symptomatology, it seems desirable to give briefly the essential anatomic changes which characterize the malady.

The schematic chart drawn by Harris and Friedrichs [23] admirably conveys to the reader in sequence the processes involved in the pathologic consideration of periarteritis nodosa:

Group 1: Injury to Vessel Wall.—This group represents the true primary lesion occurring in the arterial wall. It is characterized by exudative and degenerative processes present in the periadventitial structures, the adventia and the media and occasionally in the intima. Acute, subacute and chronic inflammatory elements may be present; also degenerative changes characterized especially by marked necrosis of the media.

Group 2: Results of Wall Injury.—Group 2 presents the phenomena attendant on severe wall injury as manifested by aneurysms, both true and false, hemorrhagic extravasations which may be the immediate cause of death and extensive thrombosis and infarction. In this group especially are the proliferative and reparative processes noted and at times organization of the thrombi. These various occurrences are the result of group 1.

Group 3: Injury of Tissue or Organs.—Herein are considered the retrograde changes present in the organs. These changes may be attributable to the curtailment of blood supply by the thrombosis present in group 2 or to pressure injury from the hemorrhagic extravasation. Cloudy swelling, fatty degeneration, coagulation necrosis or other forms of cell destruction are observed. The hemiplegia, diarrhea, nephritis and other clinical phenomena may be included in this group, which is consequent to the pathologic processes present in group 2.

Particular cognizance should be taken of the result of the damage to a vessel well, especially the aneurysmal dilatation which is at times followed by rupture and consequent hemorrhage. One should also bear in mind that the periarteritic node is often an aneurysmal outpouching rather than a mass of proliferated granulation tissue projecting from one side of a vessel wall. As a matter of fact, a modification of the term introduced by Kussmaul and Maier [1] suggested by Harris and Friedrichs,[23] namely, periarteritis nodosa aneurysma thrombotica, furnishes a more accurate description of the characteristic changes. The lesions are not of a nodose form in all cases, for diffuse thickening of the entire vessel wall is not infrequently encountered; nor are macroscopic nodose or diffuse thickenings constant accompaniments of the disease.

A complete absence of grossly demonstrable vascular lesions were found in the cases of Meyer,[32] Veszpremi[33] and Wohlwill,[34] although the microscopic changes were typical.

SYMPTOMATOLOGY

The basis of the symptoms can be readily grasped when one remembers that periarteritis nodosa, being essentially a disease of the medium-sized blood vessels, resembles, from the standpoint of the widespread distribution of the susceptible tissues, such conditions as syphilis and arteriosclerosis. The bewildering symptomatology of the disease can be rendered least intricate by assuming the presence of an infectious process which in addition to producing general disturbances such as fever, tachycardia, prostration, cutaneous eruptions and leukocytosis, causes symptoms based on circulatory disturbances in the systems or regions affected. On this basis Kroetz[35] divides the clinical manifestations of periarteritis nodosa into two groups—constitutional and local. In the first group the symptoms are indistinctive, being those of a chronic septic process with an onset which may be acute, but which is more often insidious. The temperature is irregular and mostly subfebrile, but may reach 104 or even 105 F. A remittent type of fever is not infrequently noted, the remissions at times being associated with drenching sweats. Afebrile periods are not uncommon. Rigors are exceptional, although chilliness is sometimes present. The pulse is, as a rule, disproportionately rapid even in the absence of evidence of cardiac involvement. A most conspicuous feature is a high grade secondary anemia which, when associated with progressive asthenia and emaciation, gives the patient the appearance referred to in the original description of the disease by Kussmaul and Maier[1] as chlorotic marasmus. The white cell blood count is as a rule increased, being generally between 15,000 and 30,000, at times showing a marked eosinophilia which may reach 51 per cent (Lamb[20]). The purpura especially involving the skin which is at times noted is apparently the result of the general infection. Cutaneous eruptions of various descriptions are encountered, including urticarial crops, erythema nodosum and forms described under the term purpura rheumatica.

The second group of symptoms in Kroetz' division, that is, those due to local vascular changes, are generally classified according to the

32. Meyer, P. S.: Ueber die Klinische Erkenntnis der Periarteriitis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl. klin. Wchnschr. **58**:473, 1921.

33. Veszpremi, D.: Ueber die Periarteriitis nodosa, Beitr. z. Path. Anat. u. z. allg. Pathol. **52**:476, 1912.

34. Wohwill, F.: Ueber die nur mikroscopisch erkennbare Form der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **246**:377, 1923.

35. Kroetz, C.: Zur Klinik der Periarteriitis nodosa, Deutsches Arch. f. klin. Med. **135**:311, 1921.

system involved. In an excellently organized summary of the literature until 1899, von Schrötter [36] segregated the polymorphic manifestations of periarteritis nodosa into a number of clinical types, including renal, abdominal, neuromuscular, cardiac and bronchial. It is essential, however, to bear constantly in mind the fact that, as a rule, several systems are simultaneously affected, limitation of symptoms referable to one organ being exceptional.

Although the coronary arteries are involved more frequently than any other set of vessels, cardiac symptoms are notoriously absent. Precordial pain is exceedingly rare, a noteworthy fact in view of the present current hypotheses with reference to the causation of angina pectoris. The cardiac decompensation which not infrequently occurs can most often be explained as secondary to kidney damage. The blood pressure is high in the presence of nephritis only.

Involvement of the kidney is so obstrusive in the clinical picture of the disease as to merit the major consideration in the article by Keegan [24] and in one of Gruber's [37] reports. In addition to the widespread arterial changes there is frequently extension of the periarteritic inflammation into the interstitium of the kidney, at times associated with a hematogenous glomerulonephritis (Ophüls [3]). Death due to uremia, as in both instances reported in the foregoing, is not an uncommon termination of the disease. Pain in the loin, especially in association with a ruptured aneurysm of the renal artery or its branches causing extensive perirenal hemorrhage, may be a forerunner of death.

Abdominal symptoms, especially those referable to the gastro-intestinal tract, are almost always present. Within the abdomen in order of frequency, the gastro-intestinal canal, kidneys, liver and gallbladder, spleen, pancreas, spermatic artery, diaphragm and suprarenals are affected by arterial changes. Since involvement of any one of the aforementioned structures may produce pain, it is not surprising that this symptom is by far the most frequent of the abdominal manifestations. In the presence of multiple lesions, which is the rule, it is difficult and at times impossible to designate definitely which one is responsible for the production of pain. The pain is often extremely severe, described mostly as colicky and at times as tearing. In the majority of cases it is located in the upper part of the abdomen, especially in the epigastrium, while in the remainder it tends to be diffuse. Vomiting is mentioned at some time during the course of the disease, as is also anorexia, in more than half the reports. Diarrhea or consti-

36. Von Schrötter, L.: Ueber Periarteriitis nodosa, Wien. klin. Wchnschr. **12**:404, 1899.

37. Gruber, G. B.: Zur Frage der Periarteriitis nodosa, mit besonderer Berücksichtigung der Gallenblasen-und Nieren-Beteiligung, Virchows Arch. f. path. Anat. **258**:443, 1925.

pation alone may be prominent, or the two may alternate. Melena is occasionally recorded. Peritonitis, the result of a local infarction with ulceration and perforation of the bowel, is one mode of death described. The abdominal symptoms may appear in irregular combinations and not infrequently present the picture of an acute surgical condition (discussed in the following).

A most troublesome and refractory condition is presented by involvement of the branches of the peripheral arteries. Symptoms of polyarthritis simulating the ordinary acute rheumatic fever or pains in the muscles, often of a far more excruciating nature, are encountered in most cases during the course of the disease. Involvement of the branches supplying the peripheral nerves leads to symptoms of a progressive multiple neuritis which may dominate the clinical picture. According to Wohlwill,[38] the degenerative changes in the nerves may result from the general toxemia independent of the changes in the arteries of the affected nerves. A recent review of the neurologic aspect of the disease is well presented by Balo.[39] In contradistinction to the frequency of peripheral nerve involvement, the vessels of the central nervous system are only exceptionally affected. The localization within the brain is associated with grave significance on account of the tendency of the disease to produce thrombosis and aneurysmal dilatation with rupture and hemorrhage.

The formation of nodules in connection with the cutaneous vessels is of great importance from a diagnostic standpoint. The nodes may represent either granulomatous thickenings or, as is more often the case, thrombosed aneurysmal dilatations. Rupture of the saccular outpouchings may lead to cutaneous hematomas. Along the course of the palpable arteries, such as the brachial and temporal, at times chains of nodules are felt.

The less common localizations not mentioned in the foregoing include the bronchial and exceptionally the pulmonary arteries (involvement of the bronchial mucous membrane apparently causing asthmatic symptoms is reported by Ophüls[3]), the generative organs and serous membranes.

Of particular interest to the clinician is the symptom complex generally referred to as "acute surgical belly." Pain, vomiting, tenderness, rigidity, fever and leukocytosis are not infrequently combined during the course of periarteritis nodosa, but as a rule are due to nonsurgical lesions. As a matter of fact, the average case of periarteritis

38. Wohlwill, F.: Aerztlicher Verein zu Hamburg, Sitzung vom 4 Dez., 1917, Berl. klin. Wchnschr. **55**:94, 1918.

39. Balo, J.: Ueber eine Häufung von Periarteriitis nodosa Fällen nebst Beiträgen zur Polyneuritis infolge von Periarteriitis nodosa, Virchows Arch. f. path. Anat. **259**:771, 1926.

nodosa with abdominal symptoms constitutes a surgical noli-me-tangere. On the other hand, it is not altogether rare to meet with a complication of a vascular involvement in which operative intervention is imperative. One finds reports of cases, for instance, in which perforation of an intestinal ulcer, the result of infarction of the bowel, or alarming abdominal hemorrhage from a ruptured aneurysm has occurred. The task of differentiating between the surgical and the nonsurgical abdominal manifestations in a case of periateritis nodosa, particularly when the condition is not recognized, is obviously a difficult one. The abdominal aspect, which has hitherto received but little emphasis in the literature, seems to warrant elaboration not only because of its diagnostic importance to both internist and surgeon, but also because it furnishes a valuable aid in the diagnosis of the disease if exploration is undertaken.

The abdominal conditions which periarteritis nodosa may simulate are numerous. In cases in which symptoms in the upper part of the abdomen are present, gallbladder disease, ruptured peptic ulcer or acute pancreatitis are usually considered, whereas with symptoms in the lower part of the abdomen, appendicitis is most often suspected. In a number of instances the picture presented is so perplexing that no attempt is made to diagnose the case preoperatively. Occasionally the onset of the disease is abrupt with acute abdominal manifestations, in which case the underlying condition is seldom if ever suspected. As a rule, however, the onset is insidious, and the abdominal manifestations occur in association with other more or less obscure symptoms and constitute only part of the complex clinical picture. Acute abdominal symptoms occurring in the presence of combinations of various syndromes, such as polyneuritis, polymyositis and nephritis, lead to further confusion when periarteritis nodosa is not suspected.

In both of the aforementioned case reports, upper abdominal pain and jaundice directed attention to disease in the biliary tract. In the first case the signs pointing to gallbladder disease led to a cholecystectomy and temporary improvement. The disease process, however, was not recognized at the operating table. The second patient would likewise have been subjected to a laparotomy had not the presence of delirium deterred the surgeon from undertaking immediate operation. Gruber [37] recently described a case in which cholecystectomy was performed following the diagnosis of gallbladder disease. Grossly the extirpated organ presented no evidence of periarteritis nodosa; microscopic sections, however, showed typical changes in the branches of the cystic artery. The patient died later with symptoms of uremia, and was found to have the characteristic periarteritis lesions in the kidneys. In the first of two cases described in the contribution by Klotz [21] a diagnosis of empyema of the gallbladder was made, based on signs of sepsis and acute abdominal symptoms. At the autopsy the cystic artery was found

to be thickened and thrombosed. However, the recurrent abdominal pain was presumably the result of rupture of several intrahepatic aneurysms, one of which had led to a subcapsular extravasation followed by intraperitoneal hemorrhage and death. A similar case, the third in Christeller's report with symptoms leading to a diagnosis of cholecystitis, ascending cholangitis or pancreatic apoplexy, came to autopsy with observations of multiple periarteritic nodes in the liver and a ruptured aneurysm on the under surface of the right lobe with hemoperitoneum. The gallbladder was filled with a blood coagulum similar to that found in the first case described in this paper, and here also no bleeding point was found. Chiari's [40] case of ruptured aneurysm of the cystic artery, cited as an unrecognized example of periarteritis nodosa by Gruber,[37] was an instance of aneurysm per erosionem due to an ulcerative cholecystitis unassociated with periarteritic changes.

The severity of the upper abdominal pain can be so marked as to suggest a ruptured peptic ulcer or pancreatitis. Mertens [9] describes a case in which the symptoms interpreted as those of an acute perforation led to an exploration and the discovery of slight pancreatic necrosis. The patient was exhibited during convalescence as having a classical example of acute pancreatitis. At postmortem a bilateral perirenal hematoma was found which in all likelihood was responsible for the acute manifestations. A similar picture was presented in the case of Laux.[41] The diagnosis of pancreatitis was made also in the case described by Müller.[42]

As might be anticipated, when the pain is experienced in the lower part of the abdomen, involvement of the appendix is suspected. In the second case of periarteritis nodosa described by Lamb,[20] a girl, aged 10, with lower abdominal symptoms, was operated on for acute appendicitis. At the laparotomy the appendix and peritoneal cavity were found to be normal, and no cause for the symptoms was discovered. Ophüls [3] cites an instance of periarteritis nodosa in a man, aged 38, who one week after the onset of his symptoms, which included severe abdominal pain, underwent an operation for appendicitis. He obtained only temporary relief.

Benedict's [43] case is an excellent illustration of the diagnostic dilemas in which abdominal symptoms in cases of periarteritis nodosa place even the most experienced clinicians. A woman, aged 44, with a presumptive diagnosis of appendicitis, was transferred from the med-

40. Chiari, H.: Berstung eines Aneurysmas der Arteria cystica in die Gallenblase mit tödtlicher Blutung, Prag. med. Wchnschr. **8**:33, 1883.

41. Laux, F. J.: Periarteriitis nodosa, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:582, 1925.

42. Müller, H.: Referred to by Gruber (footnote 37).

43. Benedict, H.: Ueber Periarteriitis nodosa, Ztschr. f. klin. Med. **64**:405, 1907.

ical to the surgical clinic on account of severe abdominal pain and the presence of a tumor mass in the appendiceal region. In the surgical ward the pain and swelling were found to be due to a hemorrhage in the abdominal wall which did not require surgical intervention. The development of jaundice and fever within the following two weeks might have led to a diagnosis of cholelithiasis had not the presence of subcutaneous nodules suggested a malignant condition. The patient was returned to the medical department, where excision of a nodule proved the condition to be periarteritis nodosa.

In the majority of cases, although the condition is considered surgical, a definite preoperative diagnosis is not ventured. Abdominal pain, fever and leukocytosis aroused the suspicion of a focus of abdominal suppuration in the case of Manges and Baehr.[22] At the operation the presence of the characteristic nodules along the course of the mesenteric vessels led to recognition and the diagnosis by the surgeon (Buerger) of periarteritis nodosa. Microscopic examination of a nodule removed for biopsy confirmed the opinion of the surgeon. So far as can be ascertained from the literature, this is the only case in which the diagnosis of periarteritis nodosa was confidently and correctly made at the operation table. In the case described by Keegan,[24] an exploratory operation was performed for symptoms referable to the right upper quadrant. The abdominal organs were normal, whereas exploration through a right flank incision disclosed a diseased kidney which was proved later to be the seat of periarteritic changes. In the case reported by Lemke,[44] an 11 year old boy was examined on account of abdominal symptoms. Except for the presence of a large amount of clear fluid, the abdomen was free from change. Four weeks later the child suddenly went into collapse, and died in a few minutes. The autopsy revealed in addition to lesions elsewhere a walnut-sized, perforated hematoma on the under surface of the liver. Repeated violent attacks of right hypochondriac pain led to the transfer of the patient in the case of Harris and Friedrichs[23] to a surgical ward, where an operation was deemed inadvisable on account of the poor condition of the patient. At autopsy, in addition to the nodular formations involving branches of the coronary, renal and gastro-epiploic arteries, there was a ruptured aneurysm of a kidney vessel with extensive hemorrhage into the circumrenal tissues. A group of puzzling cases with abdominal manifestations is illustrated by a case reported by Meyer,[32] in which the polyneuritic symptoms were in the foreground, although the patient complained also of gastric disorder and bloody stools, among other symptoms. On the day of death, abdominal pain, tenderness and rigidity were most prominent. At

44. Lemke, R.: Ein Beitrag zur Frage der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **240**:30, 1922.

autopsy an acute suppurative peritonitis, the result of perforation of one of the multiple disseminated ulcers of the small bowel, was discovered. The frequency of intestinal ulceration is indicated in the review of twenty cases by Meyer,[32] in ten of which defects of the wall were present.

DIAGNOSIS

The diagnosis of periarteritis nodosa in the absence of the characteristic cutaneous nodules or operative intervention is seldom correctly made. Based on the predominating symptom complex in the clinical picture, the diagnosis is usually that of sepsis, miliary tuberculosis, typhoid, trichiniasis, nephritis, an acute abdominal condition requiring surgical intervention, dysentery, polyneuritis, polymyositis, dermatomyositis, meningitis, encephalitis, cerebral hemorrhage, purpura or one of many other more or less well recognized conditions. As Lamb [20] points out, the aforementioned diagnoses are practically always made with reservations, since the clinical picture is, as a rule, atypical; furthermore, no one disease in the aforementioned group can account satisfactorily for all the symptoms usually manifested. The latter statement is borne out particularly in the abdominal group, in which, associated with the acute symptoms, are signs of extra-abdominal disease such as nephritis, polyneuritis, purpura and other conditions which cannot be logically explained by any primary surgical abdominal lesion.

The difficulty in recognizing the disease in the absence of visible lesions, aside from its rarity, is due not only to the multiplicity but also to the innumerable combinations of the symptoms. From his study of the literature, Meyer [32] considered the following triad of clinical syndromes of importance in the diagnosis of periarteritis nodosa: chlorotic marasmus, polyneuritic and polymyositic symptoms, and gastro-intestinal manifestations. To this triad, later writers are agreed (Brinkmann,[45] Christeller [6]) that nephritis should be added as a cardinal symptom. Benefiting from the experience with his first case in which the disease was first recognized at autopsy, Sacki [25] was able to predict, from the clinical symptoms described, the presence of periarteritis nodosa in a second case in which nodules were at no time discovered.

The appearance of nodules in the skin, present at one time or other in approximately 20 per cent of the cases, as a rule furnishes the first clue to and not infrequently leads to the discovery of the nature of the disease. In some cases the suspicion of the presence of periarteritis nodosa based on the clinical symptomatology causes a more careful search to be made, which is at times rewarded by the finding of the characteristic lesions. The occurrence of cutaneous granulomas and

45. Brinkmann: Zur Klinik der Periarteriitis nodosa, München med. Wchnschr. **69**:703, 1922.

aneurysmatic nodes not only allows early clinical recognition of periarteritis nodosa, but also permits, through vital excision, microscopic confirmation and proof of the presence of the disease. Through biopsy the existence of periarteritis nodosa (in some instances suspected before histologic examination) was unequivocally established in the cases of Kussmaul and Maier,[1] Schmorl,[46] Benedict,[43] von Haun,[47] Morawitz,[48] Kopp.[49] Carling and Hicks,[14] and Weigeldt.[50] Not all cutaneous or subcutaneous swellings occurring in the course of periarteritis nodosa present the typical changes, however, as observed in the case of Klotz,[21] in which a nodule on becoming fluctuant was incised and yielded a thick gelatinous material. It may be well to point out also in this connection that not all nodules along the course of superficial arteries are part of a true periarteritis nodosa, as exemplified by the case of Sabin [16] mentioned in the introductory remarks.

The revelation of the characteristic lesions in cases in which cutaneous nodes are absent occurs in instances in which operative intervention is undertaken, usually on the basis of a mistaken diagnosis. In the case of Manges and Baehr,[22] the surgeon Buerger recognized the distinctiveness of the lesions along the mesenteric vessels, and confirmed his opinion by excision and microscopic examination of one of the nodes. A painful swelling involving the right calf of their patient prompted Carling and Hicks [14] to explore the lesion. The "lumpiness" was due to a number of scattered nodules about the small arteries of the muscles associated with the presence of edema. Histologic examination disclosed typical changes. Gross evidence of periarteritis nodosa, according to Gruber,[37] was lacking in the gallbladder removed at operation and submitted to him for pathologic study, whereas the microscopic changes were classical. In the first case reported in this paper the lesions, though typical, were not recognized because of lack of acquaintance with the manifestations of the disease until some time had elapsed after the microscopic sections were examined. Under the caption of primary vascular nephritis or renal periarteritis nodosa, Keegan [24] describes a case in which a surgically removed kidney showed characteristic and rather early changes found in a more advanced stage in the opposite kidney and elsewhere at the time of death two months later.

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46. Schmorl: Diskussion zu Benda's Vortrag über Aneurysma und Syphilis, Verhandl. d. deutsch. path. Gesellsch. **6**:203, 1903.

47. Von Haun, F.: Pathologische-histologische und experimentelle Untersuchungen über Periarteriitis nodosa, Virchows Arch. f. path. Anat. **227**:90, 1919-1920.

48. Morawitz, quoted by Gruber (footnote 4).

49. Kopp, G.: Ein klinisch diagnostizierter Fall von Periarteriitis nodosa, Deutsche med. Wchnschr. **49**:1239, 1923.

50. Weigeldt: Med. Gesellsch. zu. Leipzig, Sitzung 8 Jan. 1924, München med. Wchnschr. **71**:218, 1924.

Before leaving the subject of diagnosis, it may be of value to stress Edens'[51] dictum that in an obscure case having the characteristics of a low-grade sepsis which is bacteriologically negative, and which cannot be logically classified as one of the more common conditions, the possibility of periarteritis nodosa should be entertained and a search for nodules in the skin instituted. The more bizarre and protean the manifestations of a case, the more suggestive of periarteritis nodosa does it become.

DURATION, COURSE AND PROGNOSIS

The duration of the illness judged by the clinical symptoms varies usually from a few days to several months, averaging about two months. It is important to bear in mind, however, that the lesions judged by the anatomic changes are not infrequently much older than the clinical history indicates, a fact which may account for the stated brief duration of some of the cases reported. The disease on the whole is chronic and progressive, the course being marked by irregular exacerbations and periods of remission. Occasionally, except for loss of weight and strength, the disease remains latent (Kroetz'[35] literature), death being due to an independent condition.

It was formerly accepted that periarteritis nodosa was almost invariably fatal. In a study of the forty undoubted cases collected by Klotz[21] in 1917, with the exception of Schmorl's case in which death occurred from a portal thrombosis after an interval of two years, the mortality was 100 per cent. As Klotz pointed out, this rather astounding death rate is to be viewed in the light that only the fatal cases are properly diagnosed and reported. This assumption has been borne out by subsequent experience, for in 1925 the statistics (Gruber[37]) indicated that from 10 to 12 per cent recovered. It is not unlikely, as pointed out by many writers, that lighter cases of the disease which heal without producing any severe clinical symptoms are not infrequent.

51. Edens, E.: Periarteriitis nodosa, Med. Klin. **35**:1203, 1923.

Book Reviews

THE SPECIALTIES IN GENERAL PRACTICE. By FRANCIS W. PALFREY, M.D. Cloth. Price, $6.50. Pp. 729. Philadelphia: W. B. Saunders Company, 1927.

This work is a pretentious volume of 729 pages without illustrations but well printed on excellent paper, which is fortunate, as every volume sold probably not only will be read but also will be kept on the purchaser's desk and used. It consists of eleven sections, one on each of the specialties, written in collaboration with the other members of the Faculty of Harvard Medical School. Each chapter aims to present such knowledge as the specialist thinks the general practitioner should possess concerning his field. The point of view is new, and it is surprising to note the difference between this work and the usual quiz compend or outline to help the student cram for examinations. The material here is carefully sorted, and only points of practical value are stressed. Therapy is discussed only in the conditions in which its management by the family physician would be safe and efficient. In all more difficult matters he is advised to consult a specialist. One is pleased, however, to note the number of conditions in which consultation is not suggested, and this work may be of great value in preventing much of the overstressing of the specialties and unnecessary referring of patients to specialists for trivial causes.

In general the selection of material has been excellent, although the section on dermatology treats of ills which are beyond the ken of the average physician, and such matters as lupus of the larynx or Tay's choroiditis seem rather deep for the family doctor. Also, one wonders why such an important field as neurology was entirely omitted, especially in view of the excellent section on psychiatry.

In such a volume two objects must be sought. First, to rule out all controversial material and give only facts, and second, to give only standard methods of therapy and not allow personal opinions or hobbies to find their way in. I am afraid that numerous sins against both these rules have been committed. Surely the management of normal labor by the repeated hypodermic administration of morphine and magnesium sulphate, followed by ether administered by rectum is a hobby and not a standard method (p. 311); also the advocacy of the extended thigh. Would all obstetricians agree that a high leukocyte count is of good prognostic value in puerperal sepsis (p. 318)? It is difficult to believe that the gynecologist seriously advocates the creation of vesicovaginal fistula to cure chronic cystitis or that such fistulas always heal spontaneously (p. 212).

In the section on surgery one finds instructions to use Lugol's solution in cases of toxic goiter (p. 677) and to operate at once in any case of appendicitis (p. 693), two debatable points to say the least. Finally, it is the unanimous opinion of specialists that if one defers the operation of cleft palate until the child is 2 or 3 years old, as advised here, normal voice is seldom attained. Likewise it is not true that cleft palate does not interfere with nursing (p. 663).

Since this review is for an American Medical Association publication, one must comment on the choice of drugs. Will witch hazel cure milk leg; cologne water, cracked breasts; or flaxseed poultices, breast abscesses?

However, these criticisms should not detract from the importance of a valuable book. I anticipate many editions and hope to see a real standard arrived at.

A Statistical Survey of 3,000 Autopsies. By William Ophüls, M.D., Stanford University, California. Price, $2.50. Pp. 370. Palo Alto, Calif.: Stanford Univ. Press, 1927.

This monograph is number 3 in the medical series of the Stanford University publications. It is a study based on the results of 3,000 postmortem examinations performed during the years from 1900 to 1923 by Dr. Ophüls and his associates at the Lane and San Francisco Hospitals at San Francisco. In such autopsies gross and microscopic examinations were made of the viscera as a routine. Bacteriologic examinations were made only in cases in which this seemed to be indicated by the nature of the case. A careful and detailed analysis of these 3,000 cases is presented. This is done chiefly by means of charts, of which there are about sixteen, as well as by numerous short tables. The diseases and lesions are classified and named according to the first edition of the "Standard Nomenclature of Diseases and Pathological Conditions, Injuries and Poisonings" issued by the United States Department of Commerce, Bureau of Census, 1920. In the analysis comparisons have been drawn freely between his data and those of other institutions, especially those of life insurance companies.

Dr. Ophüls deserves credit for this painstaking analysis, for it is based on data obtained at the autopsy table and therefore should be much more reliable than masses of data of this sort presented purely from the clinical standpoint.

Attention may be called to a number of interesting points. The fact is brought out that careful search revealed anatomic evidence of acquired syphilis in 9.5 per cent of all cases (11 per cent of adults). In the majority of the cases, these changes appeared in the aorta.

Under the caption "Infectious Diseases," it is noted that the most numerous deaths were those from diphtheria (1.5 per cent of all cases). This reveals what still remains to be done in the control of a disease about which apparently so much is known; yet physicians appear to be helpless so far as applying that knowledge in a way that rapidly reduces the mortality is concerned. The work is unique, too, because of the large number of cases of certain rare infections reported; for example, coccidioidal granuloma (seven cases). Nowhere but in California could such a large series of cases of this disease be encountered.

This monograph should be of real service to both pathologists and clinicians, not only in connection with an analysis of their own work, but also from the point of view of comparing the occurrence of various lesions and diseases in different parts of the country.

Mention should be made of the fact that during the past twenty years. Dr. Ophüls has made many contributions to the literature, and he has based his intensive studies on the material that is here analyzed. In this connection, one may refer to his work on nephritis and arteriosclerosis.

Studies on Acidosis. By Dautrebande, Labbe and Nepveux, and Petren. Transactions of the French Congress of Medicine, 18th Session, 1925.

In the first part of this exhaustive report, Dautrebande discusses fully the modern conception of acidosis as developed by the American, English and Danish physiologists and biochemists (Van Slyke, Y. Henderson, Haldane,

Barcroft, Hasselbach and others), and includes an explanation of the physiologic mechanism by which acid-base equilibrium is maintained.

In the second part of the paper, contributed by Labbe and Nepveux, methods for the determination of acid-base equilibrium, both direct and functional, are given and compared from the standpoints of ease of manipulation and of relative value.

The third contribution, by Petren, deals with the pathologic physiology of acid-base equilibrium, and in it are discussed the causes of the acidoses found in emphysema, pulmonary tuberculosis, bronchial asthma, bronchial pneumonia, pneumothorax, morphine administration, diabetes, nephritis, enteritis, cyclic vomiting of children, pregnancy, pernicious vomiting of pregnancy, prolonged fasting, anesthesia, lobar pneumonia, shock (traumatic, infectious and anaphylactic) peptic ulcer, various circulatory disturbances and other less important conditions. The literature of acidosis is reviewed in relation to each of the conditions mentioned.

The report as a whole is an excellent exposition of the modern view of acidosis and a thorough review of the literature on the subject. The author is frank in giving credit to contributors on this subject when credit is due. The bibliography refers to more than 300 articles.

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CONTENTS

PAGE

Studies in Acromegaly: VI. The Disturbances of Carbohydrate Metabolism. Leo M. Davidoff, M.D., and Harvey Cushing, M.D., Boston 751

The Influence of Menstruation on the Concentration of Calcium in Blood Plasma. Herman Sharlit, M.D.; James A. Corscaden, M.D., and William G. Lyle, M.D., New York 780

The Protein Test for Urea Formation Function of the Liver: Preliminary Report. Philip Cohen, M.D., New York, and S. J. Levin, M.B., Ann Arbor, Mich 787

The Diameter of Red Blood Cells in Health and in Anemia: New Method of Measurement. A. R. McCormick, M.D., Pittsburgh 799

Cerebrospinal Fluid in Nephritis. John D. Lyttle, M.D., and Lester Rosenberg, M.D., Assisted by John E. Hearn, New York 808

The Toxic Action of Cystine on the Kidney. A. C. Curtis, M.D., and L. H. Newburgh, M.D., with the Technical Assistance of F. H. Thomas, M.D., Ann Arbor, Mich ... 817

The Toxic Action of Cystine on the Liver of the Albino Rat. A. C. Curtis, M.D., and L. H. Newburgh, M.D., Ann Arbor, Mich 828

War Gases and Tuberculosis: An Experimental Study. A. R. Koontz, M.D., Edgewood, Md 833

Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations: Report of Two Cases. Harry A. Singer, M.D., Chicago 865

Book Reviews 890

General Index 893